Cethromycin for the Treatment of Community-Acquired Bacterial Pneumonia

FDA Briefing Document for
Anti-Infective Drugs Advisory Committee Meeting
June 2, 2009

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I. BACKGROUND

Advanced Life Sciences, Inc. submitted New Drug Application (NDA) 22-398 for RESTANZA™ (cethromycin) tablets on September 30, 2008. Cethromycin is a ketolide antibacterial drug, similar to telithromycin, which is the only approved ketolide. Ketolides are related to macrolide antibacterials, including erythromycin and clarithromycin. The proposed indication for cethromycin is treatment of mild to moderate community-acquired bacterial pneumonia (CABP) due to susceptible strains of *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Moraxella catarrhalis,* and *Legionella pneumophila* in patients 18 years of age and older. The FDA has recently proposed the name community-acquired bacterial pneumonia, as part of a draft guidance document, to focus on the pneumonia in patients with documented bacterial infections. The reader is referred to Appendix 1 for a copy of the draft guidance.

The drug product is an immediate-release tablet containing 150 mg of cethromycin. The proposed dose of cethromycin is two tablets (300 mg) once daily for seven days.

This briefing document summarizes the information submitted in the cethromycin NDA. The last section of this document (**VIII**) highlights the expected issues for advisory committee discussion.

II. CLINICAL DEVELOPMENT

The investigational new drug application (IND 57,836) for cethromycin (aka ABT-773) was submitted by Abbott Laboratories on February 2, 1999. The sponsor conducted phase 1 and some phase 2 studies under the IND, including some pilot studies of community-acquired pneumonia, acute bacterial exacerbation of chronic bronchitis, pharyngitis, and sinusitis. Studies under the IND were conducted by Abbott Laboratories between 1999 and 2002, when Abbott discontinued further development of the product. There were two multi-national dose-ranging studies of cethromycin for CABP. These were phase 2 studies comparing without active controls. One study compared 300 mg and 600 mg daily, but was stopped early. The second study used 150 mg once daily or twice daily. A third dose-ranging study of a small number of patients was conducted in Japan. None of these studies conducted by the original IND sponsor provide substantial evidence of effectiveness for CABP, but all of the Abbott studies contribute some information on the safety of cethromycin.

IND sponsorship was transferred to Advanced Life Sciences, Inc. in 2005. The new sponsor intended to develop cethromycin for treatment of community-acquired pneumonia as the sole indication for the NDA submission. Two multicenter, randomized, double-blind non-inferiority studies of community-acquired bacterial pneumonia were discussed with Division at the end of 2005. Advanced Life Sciences,

Inc. also performed a new study to evaluate QTc prolongation; the prior study conducted by Abbott Laboratories was incomplete because of liver function test abnormalities reported in some participants. These clinical trials were submitted in the NDA application for cethromycin on September 30, 2008.

There have been recent discussions of clinical trial design for CABP studies, including a workshop in January of 2008, and a meeting of the Anti-Infective Drugs Advisory Committee on April 1, 2008. While the NDA submission for cethromycin occurred after the discussions of clinical trials for CABP, it should be noted that the trials completed enrollment in 2007.

Subsequent to these discussions, FDA has issued a draft Guidance on developing drugs for treatment of CABP. The draft Guidance document was published in March of 2009, and is included as Appendix 1 of this package. Since this document is still in draft form, the FDA is currently receiving comments from interested parties on the guidance. The document may undergo significant future revisions prior to being issued in final form.

III. PHARMACOLOGY-TOXICOLOGY

A battery of safety pharmacology studies was performed, including examination of effects on the nervous system in mice and rats, the cardiovascular system *in vitro* and *in vivo* in anesthetized and conscious dogs, the respiratory system in rats, and the gastrointestinal system *in vitro* in rabbit and guinea pig tissues and *in vivo* in mice. Single oral doses to rats or mice resulted in alteration of motor activity, decrease in body temperature, and decreased latency to induced tonic convulsions. Cardiac safety studies indicated potential for effects on the heart, including QT prolongation, *in vitro* and *in vivo*. In the *in vitro* hERG assay, the IC_{50} for blockage of hERG tail current was 22.1 μg/mL, resulting in a hERG index similar to or less than that of other antibiotics for which cardiac repolarization effects are a concern, including telithromycin. Prolongation of action potential duration *in vitro* was greater than that for other drugs of concern. In conscious telemetered dogs, all doses (3, 10, or 30 mg/kg, administered IV as a 30-minute infusion) resulted in significant increases in systolic and diastolic arterial pressure. PR interval was increased at the mid-dose. At the high dose, QT and QTc were increased, as well as PR interval and blood pressure. Maximal increases in parameters were seen at 90-115 minutes post-dose. In a respiratory study in rats, minute volume was decreased. Potential for alteration of smooth muscle contraction and transit time in the gastrointestinal tract was demonstrated.

Two-week IV toxicology studies were performed in rats, cynomolgus monkeys and dogs. Severe irritation at the injection site was observed and was accompanied by increased white blood cell counts and bone marrow myeloid hyperplasia (and thymic lymphoid atrophy in rats). All three species exhibited anemia with evidence of regeneration. Clinical chemistry analysis revealed evidence of adverse liver effects and was accompanied by histological evidence (biliary hyperplasia, multifocal coagulative

necrosis, hepatocellular vacuolation) in dogs. BUN was increased in rats, and dark material was found in the gastrointestinal tract in that species. Changes to the ECG, including QTc prolongation were seen in monkeys and dogs. Testicular toxicity was observed in rats and monkeys. Drug accumulation was evident with repeated dosing by the IV route.

Repeated dose toxicity studies by the oral route were performed for 2 weeks, 1 month, and 3 months in rats and in cynomolgus monkeys. A 4-week toxicology study of oral cethromycin was conducted in juvenile rats. A number of common effects were observed, including: body weight loss and decreased food consumption, evidence of regenerative anemia (decreased red blood cell parameters, increased reticulocytes, and/or bone marrow hypercellularity), irreversible testicular atrophy/degeneration with spermatid degeneration or aspermia at the highest tested doses (adverse effects confirmed in male fertility testing in rats), and histological and ultrastructural findings in the lung and liver that were consistent with phospholipidosis.

Additional findings were seen in rats, including lymphoid depletion and/or necrosis of the spleen, thymus, and lymph nodes at 500 mg/kg/day for 2 weeks. Findings possibly reflecting effects on liver function included decreases in total protein and/or albumin at all doses in females and high dose males, and increases in serum transaminases, and/or total bilirubin at the higher doses in the 1- and 3-month studies. Liver weight was increased in the 1- and 3-month studies at doses of 60 mg/kg and above and persisted in recovery groups. Histological examination of animals in the 3-month study revealed multinucleated hepatocytes, bile duct proliferation and cholangiofibrosis at all doses, and ultrastructural examination of recovery animals (only the high dose group was examined) in the 1-month study revealed autophagic vacuoles in the liver. Glucosuria was noted in all 3 studies at doses of 60-180 mg/kg/day. Kidney weights were increased in the 3-month study, and ultrastructural evidence consistent with phospholipidosis was found in that organ at the high dose for 1-month and all doses for 3 months. Deaths occurred at 160 mg/kg/day and above.

Additional findings in juvenile rats included increased mortality, convulsions and ptosis at 180 mg/kg/day. Serum ALT, alkaline phosphatase, and GGT were increased at all doses. Serum albumin was decreased and liver weights were increased at 60 and 180 mg/kg/day. Minimal diffuse hepatocellular hypertrophy and electron microscopic findings consistent with phospholipidosis were noted at the high dose. Gastrointestinal findings included dark areas in the cecum, dilation of stomach and intestines, and necrosis in the cecum. It is notable that Cmax and AUC were approximately twice as high as those values determined in the 4-week toxicity in older animals.

Deaths occurred in cynomolgus monkeys at 70 mg/kg/day and above in the 1- and 3-month studies. Additional findings in this species included emesis at doses of 50 mg/kg/day and above. Dilated gastric glands with necrosis and/or hemorrhage were seen in early decedents in 1-month study. Increased BUN and/or creatinine with electrolyte alterations were observed at all doses for as little as 2 weeks. Degeneration of distal

convoluted tubules with mononuclear cell infiltration was seen microscopically at doses of 70 mg/kg/day and above for 2 weeks, although renal findings were limited to increased kidney weight at the high dose in the 1-month study with no histological correlates, and there were no significant renal findings in the 3-month study. Increased serum ALT and/or AST was found at 200 mg/kg/day in the 2-week study, at 200/140 mg/kg/day after 2 weeks in the 1-month study, at 25 and 70 mg/kg/day at the end of the 1-month study, but only at 50 mg/kg/day and above in the 3-month study. Ultrastructural evidence of phospholipidosis at 70 mg/kg/day and above was seen in the 1-month study. Additionally, in the 3-month study, increased liver weight and hepatocellular and Kupffer cell pigmentation were observed histologically; these findings persisted through the recovery period. There were GLP compliance issues with the 1- and 3-month monkey studies that leave the reliability of the data from those two studies in question.

In each of the three rat oral toxicology studies, the lowest dose, 20 mg/kg/day (HED = 3.3 mg/kg/day) was considered the NOAEL or LOAEL. Findings at that dose were limited to decreased albumin and increased APTT after 2 weeks' or 1 month's treatment, but included increased kidney weight and some ultrastructural pathological findings in liver and kidney after 3 month's treatment (described above). Toxicokinetic monitoring in rat studies indicated that the Cmax at this dose ranged from 0.359 to 2.5 μg/mL, and AUC values ranged from 4.65 to 24.5 μg·hr/mL, with higher values for both parameters generally seen with increasing duration of treatment and in females relative to males. At that dose in the 4-week juvenile rat study, the mean Cmax = 1.3 μg/mL, and the AUC = 12 μg·hr/mL, and toxicological findings were of greater severity.

In each of the three monkey oral toxicology studies, the lowest dose, 25 mg/kg/day (HED = 8.3 mg/kg/day) was considered the NOAEL or LOAEL. Findings at that dose were limited to increased BUN and creatinine after 2 weeks treatment, anemia / reticulocytosis, increased AST/ALT, and histological findings of foamy macrophages in the lung (consistent with phopholipidosis) after 1 month's treatment, and no reported adverse findings after 3 months' treatment. Toxicokinetic monitoring in monkey studies indicated that the Cmax at this dose ranged from 0.23 to 1.2 μg/mL, and AUC values ranged from 2.8 to 10.1 μg·hr/mL, with higher values for both parameters generally seen with increasing duration of treatment.

IV. MICROBIOLOGY

Summary of Microbiology Findings

- Cethromycin inhibits protein biosynthesis by binding to the 23s ribosomal RNA of the 50s ribosomal subunit of the bacterial ribosome. This binding results in a prolonged *in vitro* postantibiotic effect (PAE).
- Cethromycin susceptibility decreases in isolates expressing either *erm* or *mef* genes, however, inhibition of these organisms is still achieved at concentrations <1 μg/mL, suggesting that cethromycin may be useful in the treatment of some macrolide-resistant organisms.

- Surveillance studies demonstrate that the spectrum of activity of cethromycin includes many organisms indicated in community-acquired pneumonia (CAP) including *S. pneumoniae* and *H. influenzae.*
- Cethromycin is bactericidal *in vitro*, generally at concentrations equal to 2-8X MIC. Cethromycin killing appears reduced for some isolates of pneumococci that harbor the *ermB* gene, although the compound is bactericidal for others. However, bactericidal activity was observed for streptococci containing *mef*, *mefA* and *mefE* genes. Bactericidal activity was evident in medium containing 50% human serum.
- Cethromycin is synergistic with doxycycline against key CAP organisms. No antagonism was noted.
- Cethromycin's antibacterial activity is concentration-dependent, with AUC_{0-24} free/MIC and Cmax/MIC are the best indicators for *in vivo* efficacy.
- In animal models of efficacy, cethromycin demonstrated efficacy against the most prevalent respiratory pathogens including *S. pneumoniae, H. influenzae*, and against many macrolide- and penicillin-resistant isolates of *S. pneumoniae*.
- Clinical and bacteriological success rates in patients treated with cethromycin were comparable to patients treated with clarithromycin when patients were infected with *S. pneumoniae* or *H. influenzae*.
- There was no apparent MIC trend in clinical or bacteriological success rates among patients infected with the target pathogens for the CAP indication.

Mechanism of Action

Cethromycin exerts its antimicrobial action by binding to the 23s ribosomal RNA of the 50s ribosomal subunit of the bacterial ribosome, stimulating the dissociation of peptidyl-tRNA from the ribosome during the translocation process, and ultimately, inhibiting protein synthesis. The interaction of cethromycin with the bacterial ribosome has been confirmed by *in vitro* binding studies with ribosomes isolated from both *S. pneumoniae* and *H. influenzae*. The tight binding characteristics of cethromycin confer rapid association to the binding site, slower dissociation from the active site, and prolonged post-antibiotic effect (PAE). This enhanced degree of interaction at the ribosomal level has resulted in antibacterial activity for cethromycin, including inhibition of bacterial protein synthesis in both macrolide-susceptible and -resistant bacteria. Cethromycin demonstrates activity against macrolide resistant pneumococci expressing either Erm methylases or efflux pumps.

Mechanisms of Resistance

Selection for cethromycin resistance has been demonstrated *in vitro* through passage experiments at either subinhibitory concentrations or at multiples of the MIC for a variety of pathogens. Cethromycin susceptibility decreases in isolates expressing either *erm* or *mef* genes, however, inhibition of these organisms is still achieved at concentrations < 1 μg/mL, suggesting that cethromycin may be useful in the treatment of some macrolide-resistant organisms. Cethromycin may be a weak inducer of *ermA* and *ermC*. In general, there is cross resistance between cethromycin and telithromycin, although some telithromycin-nonsusceptible *S. pneumoniae* were more sensitive to cethromycin. High

levels of constitutive Erm methylase expression, obtained through mutations in the upstream regulatory region, lead to high-level cethromycin, telithromycin, and MLS_B resistance.

Cethromycin has not been shown to induce self-resistance. There were no isolates that developed resistance to cethromycin during the conduct of clinical trials.

Spectrum of Activity

Cethromycin was evaluated in several multinational surveillance studies in 2004-2007, concentrating on pathogens likely to be found in CAP. MICs of cethromycin for nearly 6000 organisms were determined using broth microdilution methodology. Susceptibility to cethromycin was compared among the various Gram-positive organisms responsible for CAP (Table 4.1).

Table 4.1: Comparative Summary of Cethromycin Activity

			MIC (µg/ml)		
Organism	**Category**	**N**	**Range**	**MIC50**	**MIC90**
S. pneumoniae	all	2499	≤0.0005-1	0.004	0.06
	Pen S	1273	≤0.0005-1	0.004	0.03
	Pen I	859	≤0.0005-0.5	0.004	0.06
	Pen R	367	0.001-0.25	0.03	0.12
	Eryth S	1724	≤0.0005-0.03	0.004	0.008
	Eryth NS	775	≤0.0005-1	0.03	0.12
S. pyogenes	All	241	0.002-1	0.008	0.008
	Eryth S	226	0.002-0.015	0.008	0.008
	Eryth NS	15	0.008-1	0.008	0.5
S. aureus	All	426	0.015->32	0.06	>32
	Ox S	162	0.015->32	0.03	0.06
	Ox R	264	0.015->32	0.06	>32
	Telith S	314	0.015-0.25	0.03	0.06
	Telith NS	112	0.5->32	>32	>32
H. influenzae	All	1671	≤0.03->32	2	4
	beta-lactamase neg.	1203	≤0.03->32	2	4
	beta-lactamase pos.	468	≤0.03->32	2	4
M. catarrhalis	All	304	≤0.015-0.5	0.06	0.12
	beta-lactamase neg.	20	≤0.015-0.12	0.06	0.06
	beta-lactamase pos.	284	≤0.015-0.5	0.06	0.12

Source: Table 44, Microbiology Section this submission.

For *S. pneumoniae*, cethromycin was active against penicillin-susceptible (PSSP), penicillin-intermediate (PISP), and penicillin-resistant (PRSP) isolates with MIC90 values of 0.125 µg/mL or less. Cethromycin inhibited erythromycin-resistant isolates, including those with defined *erm*(B), *mef*(A,E), and ribosomal mutations at 0.50 µg/mL or less. Cethromycin yielded MIC90 values of 4 µg/mL for *H. influenzae*, regardless of whether the isolates were β-lactamase-negative or –positive, or whether they were β-lactamase positive but ampicillin-resistant. The compound was active against *M.*

catarrhalis with MIC90 values of 0.12 μg/mL or less regardless of whether the isolates were β-lactamase negative or –positive.

Bactericidal Activity
The bactericidal activity of cethromycin has been evaluated against multiple isolates of *S. pneumoniae* (including isolates containing *erm*, *ermB*, *mef*, and *mefE*), *H. influenzae*, *M. catarrhalis*, *C. pneumoniae*, *L. pneumophila*, *M. pneumoniae* and *S. pyogenes* (including isolates containing *ermTR* and *mefA*). The majority of the assays were conducted at concentrations of 2- and 8-fold MIC. In general, killing at 8-fold MIC was greater than that achieved at 2-fold MIC. At 8-fold MIC, cethromycin was bactericidal against many of the test isolates, including both macrolide-susceptible and –resistant isolates, with some modest variability between similar studies. Cethromycin killing appears reduced for some isolates of pneumococci that harbor the *ermB* gene, although the compound is bactericidal for others. Likewise, the compound was not bactericidal for *S. pyogenes* isolates containing the *ermTR* gene. Bactericidal activity was observed for streptococci containing *mef*, *mefA* and *mefE* genes. Overall, cethromycin demonstrated superior killing properties relative to the macrolides and azalides. Bactericidal activity was also evident in medium containing 50% human serum demonstrating that the activity of cethromycin was manifested even though the molecule has a relatively high percentage of serum protein binding.

Interactions with other Antimicrobials
In vitro interaction studies of cethromycin with other antimicrobials (e.g., azithromycin, trimethoprim/sulfamethoxazole, rifampin, doxycycline, amoxicillin/clavulanic acid, linezolid, ceftriaxone, levofloxacin, ciprofloxacin, vancomycin, imipenem) do not indicate a potential for antagonistic effects when tested against *S. pneumoniae, S. aureus, S. pyogenes, H. influenzae* or *M. catarrhalis. In vitro* interaction studies indicate a moderate synergistic effect when cethromycin is combined with doxycycline when tested against key CAP organisms.

Pharmacokinetics and Pharmacodynamics
Animal pharmacodynamic studies have shown that cethromycin's antibacterial activity is concentration-dependent, with $AUC_{0\text{-}24}$ free/MIC and Cmax/MIC being the best indicators for *in vivo* efficacy.

Cethromycin accumulates in lung tissue, which would produce higher intrapulmonary Cmax/MIC and AUC/MIC ratios and prolonged %T > MIC values, supporting a QD dosing regimen for the treatment of respiratory infections. Based on the ratios determined from animal models, cethromycin dosed at 300 mg QD for 5 days exceeded the predicted values for 3 of the 5 groups of pathogens in plasma, 4 of the 5 groups in epithelial lining fluid (ELF), and all 5 groups in alveolar cells (AC).

Efficacy in Animal Infection Models
Cethromycin demonstrated efficacy against the most prevalent respiratory pathogens including *S. pneumoniae, H. influenzae*, and against many macrolide- and penicillin-

resistant isolates of *S. pneumoniae*. Cethromycin was also effective against infections in salient anatomical locations such as the systemic (septic), inner ear (bullae), pulmonary, and skin (abscess) body systems, with excellent activity against fluoroquinolone-resistant *S. pneumoniae* in a thigh infection model in neutropenic rats. QD dosing was found to be as effective as BID dosing in the treatment of rat pulmonary infections.

Clinical and Microbiological Efficacy at TOC by MIC
There was no apparent MIC-related trend in clinical or bacteriological outcomes among patients infected with the target pathogens for the CAP indication (see Appendix 2). In addition, there were relatively few isolates with cethromycin MICs > 0.25 µg/mL; the exception to this were *H. influenzae* isolates; most of these isolates had MICs ≤ 8 µg/mL. There was no apparent zone diameter-related trend in clinical success rates or bacterial eradication rates, respectively, among patients infected with the target pathogens for the CAP indication.

Proposed Susceptibility Breakpoints
The Applicant proposes the following susceptibility breakpoints for cethromycin. These breakpoints are currently under review by the Agency.

Table 4.2: Proposed Cethromycin Susceptibility Breakpoints

Organism	MIC (µg/mL)			Zone Diameter (mm)		
	S	I	R	S	I	R
Streptococcus pneumoniae	≤ 0.25	0.5	≥ 1	≥ 19	16 – 18	≤ 15
Haemophilus influenzae	≤ 8	16	≥ 32	≥ 15	12 - 14	≤ 11
Staphylococcus aureus	≤ 0.5	1	≥ 2	≥ 22	19 - 21	≤ 18
Moraxella catarrhalis	≤ 0.5	--[a]	--[a]	≥ 25	--[a]	--[a]

[a] Intermediate and Resistant categories are not defined due to the absence of resistant isolates
Source: Table 134, Microbiology section, this submission.

V. CLINICAL PHARMACOLOGY

5.1 Summary of Pharmacokinetic Characteristics of Cethromycin

5.1.1 General Pharmacokinetics
Cethromycin demonstrates non-linear pharmacokinetics, with more than dose-proportional increase in exposure. Non-linear and time-dependent pharmacokinetics were observed in healthy non-Japanese adult males following single and multiple once-daily (up to 5 days) doses of 150, 300, and 600 mg. Steady state concentrations were achieved by the third daily dose.

Mean pharmacokinetic parameters of cethromycin following single and multiple (QD for 5 days) oral doses of 150, 300, and 600 mg are summarized in **Table 5.1**.

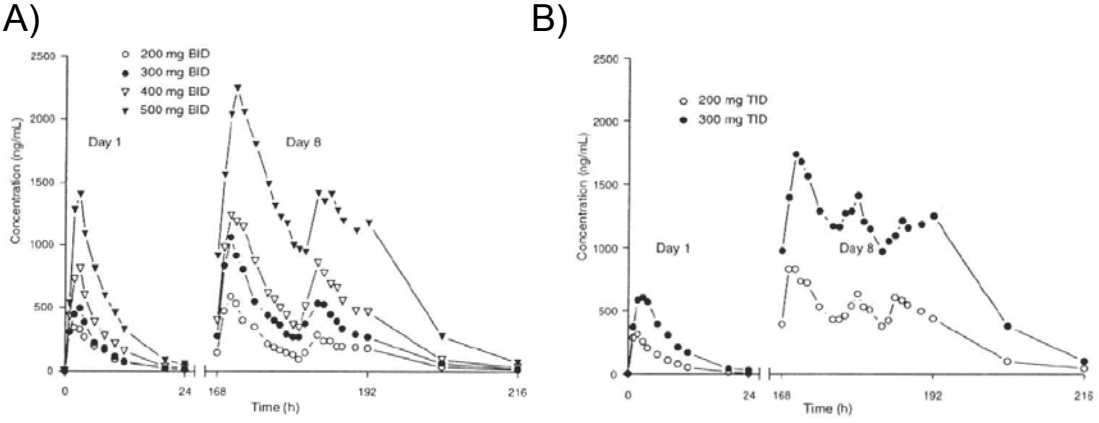
Table 5.1 Pharmacokinetic parameters of cethromycin in healthy non-Japanese adult males

	150 mg (n=12)	**300 mg** (n=12)	**600 mg** (n=12)
	Single Dose		
AUC_{24} (ng•h/mL)	1873 ± 686	6393 ± 2894	12864 ± 3130
C_{max} (ng/mL)	439 ± 171	967 ± 488	1620 ± 433
T_{max} (h)	1.5 ± 0.7	1.9 ± 1.2	2.9 ± 0.9
$t_{1/2}$ (h)	5.72 ± 1.61	6.80 ± 1.36	5.69 ± 1.00
V_β/F (L/kg)	10.19 ± 5.18	7.39 ± 3.22	5.40 ± 1.84
CL/F (L/h/kg)	1.19 ± 0.49	0.72 ± 0.26	0.61 ± 0.15
	Multiple Dose (QD × 5 days)		
AUC_{24} (ng•h/mL)	2347 ± 824	6449 ± 2100	17011 ± 5012
C_{max} (ng/mL)	498 ± 295	1023 ± 377	2137 ± 745
T_{max} (h)	1.1 ± 0.6	2.3 ± 1.4	2.9 ± 1.2
C_{min} (ng/mL)	9.56 ± 3.06	30.04 ± 18.32	117.78 ± 37.55
$t_{1/2}$ (h)	7.29 ± 2.33	6.93 ± 2.27	7.43 ± 1.12
V_β/F (L/kg)	9.39 ± 4.11	6.27 ± 1.98	5.05 ± 1.43
CL/F (L/h/kg)	0.91 ± 0.29	0.69 ± 0.29	0.47 ± 0.13

Cethromycin pharmacokinetics exhibit diurnal variation, with higher concentrations following doses administered in the morning than in the afternoon or evening. Diurnal effect was apparent when doses were administered BID (morning, evening) or TID (morning, afternoon, midnight) in healthy adult males.

Mean concentration-time profiles of cethromycin following single and multiple BID or TID doses of 200-500 mg are shown in Figure 5.1.

Figure 5.1 Concentration-time profiles of cethromycin in healthy adult males for **A)** BID and **B)** TID dosing regimens



5.1.2 Absorption

There was no significant food effect observed when cethromycin was administered with a high-fat meal compared to fasting conditions.

5.1.3 Distribution

In human plasma, the protein binding of cethromycin is approximately 90-96%. Binding is primarily to α_1-acid glycoprotein, and is concentration-dependent in an inverse manner. Protein binding is not affected by severe renal insufficiency or mild/moderate hepatic impairment.

Intrapulmonary penetration of cethromycin into epithelial lining fluid (ELF) and alveolar cells (AC), as AUC_{ELF}/AUC_{plasma} and AUC_{AC}/AUC_{plasma} ratios were 7.9 and 207, respectively, in healthy adults following 300 mg QD for 5 days. Mean ELF concentration was 6.7 ± 3.4 μg/mL at the end of the 24-hour dosing interval, while mean AC concentration was 0.1 ± 0.1 μg/mL at 24 hours.

5.1.4 Metabolism

In vitro experiments with human liver microsomes and recombinant CYP isoforms indicate that cethromycin is metabolized to one primary metabolite (M-1) and two secondary metabolites. The M-1 metabolite is formed by CYP3A (both CYP3A4 and CYP3A5 are able to metabolize cethromycin). Further *in vitro* work demonstrated that cethromycin was able to inhibit CYP3A-dependent nifedipine oxidation with an IC_{50} of 0.63 μM (482.5 ng/mL).

Seven metabolites of cethromycin were identified in a mass balance study of healthy adult males with radiolabelled cethromycin, with the predominant metabolite accounting for 20% of the radioactivity in plasma and <10% of the radioactivity in urine. The major metabolite (M1), *N*-desmethylcethromycin, is approximately 25% that of the parent drug and possesses less pharmacological activity than cethromycin.

5.1.5 Excretion

Cethromycin is primarily eliminated via the feces, with 31% of the administered dose recovered unchanged in the stool and 6% of the dose recovered unchanged in urine, based on radioactivity (collected up to 168 hours) from a mass balance study. Elimination is complete by 96 hours.

5.2 Effects of Intrinsic Factors on Cethromycin PK

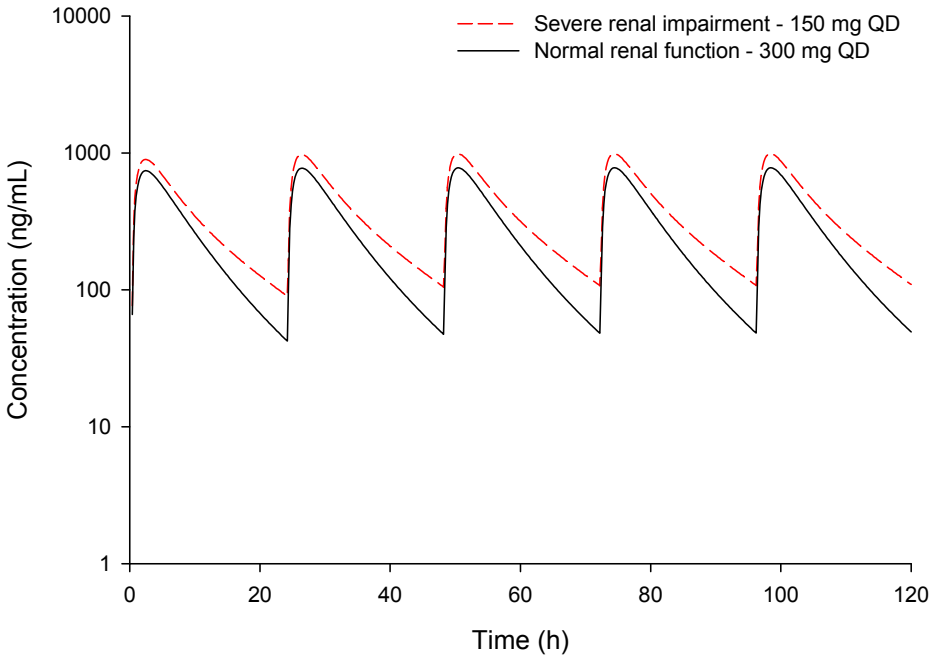
5.2.1 Renal Impairment

Pharmacokinetics of cethromycin were evaluated in subjects with normal renal function (CrCL >80 mL/min) and severe renal impairment (CrCL 10-29 mL/min) following 300 mg QD for 5 days. Mean C_{max}, AUC_{24}, and C_{min} values of subjects with severe renal impairment were 2.7, 2.9, and 4.0 times those of subjects with normal renal function, respectively. Based on these data, a reduced dose of 150 mg

QD was simulated using pharmacokinetics of subjects with severe renal impairment (see Figure 5.2).

A dose adjustment of 150 mg QD is recommended for patients with severe renal impairment. Cethromycin has not been evaluated in subjects with mild (CrCL 50-80 mL/min) or moderate (CrCL 30-50 mL/min) renal impairment, or dialysis, and as such, there are no dose recommendations available for these patient populations.

Figure 5.2 Mean concentration-time profiles of cethromycin for 150 mg QD × 5 days in subjects with severe renal impairment (CrCL 10-29 mL/min) versus 300 mg QD × 5 days in subjects with normal renal function (CrCL >80 mL/min)



5.2.2 Hepatic Impairment

Pharmacokinetics of cethromycin were evaluated in subjects with normal hepatic function, mild hepatic impairment (Child-Pugh Class A), and moderate hepatic impairment (Child-Pugh Class B), following 300 mg QD for 5 days. Steady-state C_{max}, AUC_{24}, and C_{min} values for subjects with mild hepatic impairment were 0.83, 0.92, and 1.05 times that of subjects with normal hepatic function, respectively. For subjects with moderate hepatic impairment, C_{max}, AUC_{24}, and C_{min} values were 0.86, 1.24, and 2.98 times that of subjects with normal hepatic function, respectively. No dose adjustments are recommended for patients with mild or moderate hepatic impairment. Cethromycin has not been evaluated in subjects with severe hepatic impairment (Child-Pugh Class C).

5.3 Drug Interaction Assessment

I*n vitro* studies using human liver microsomes have demonstrated that cethromycin is a substrate and an inhibitor of CYP3A. Another *in vitro* study has shown that cethromycin is able to inhibit the transport of vinblastine across a polarized epithelial monolayer of Caco2 cells. Cethromycin is therefore an inhibitor of P-glycoprotein (P-gp). The same study also strongly suggested that cethromycin is a substrate of P-gp, which would likely influence its absorption and distribution.

5.3.1 Rifampin

Cethromycin co-administration with rifampin, a known inducer of CYP3A, reduced the C_{max} by more than 92% compared to when cethromycin was administered alone. Similarly, the AUC_{∞} of cethromycin was reduced by nearly 95% when co-administered with rifampin. Cethromycin should not be co-administered with strong CYP3A inducers.

5.3.2 Ketoconazole

When ketoconazole, a known inhibitor of CYP3A, was co-administered with cethromycin, the mean cethromycin C_{max} was 2.6 times the value obtained with cethromycin alone. The AUC_{∞} of cethromycin co-administered with ketoconazole was 4.9 times the value of obtained with cethromycin alone. A dose adjustment of cethromycin will likely be required with administration of strong CYP3A inhibitors.

5.3.3 Midazolam

When cethromycin was co-administered with midazolam, a known substrate of CYP3A, the mean midazolam C_{max} was 1.5 times the value obtained with midazolam alone. The AUC_{∞} of midazolam when co-administered with cethromycin was 2.3 times the value obtained with midazolam alone. Dose adjustment of other drugs which are CYP3A substrates may be required upon co-administration with cethromycin.

5.3.4 Other

Other drug interaction studies were conducted with theophylline, warfarin, digoxin, and ethinyl estradiol and norethindrone. No dose adjustments of theophylline, warfarin, digoxin, or ethinyl estradiol and norethindrone were found to be necessary due to interactions between cethromycin and any of the above drugs. However, continued plasma concentration monitoring is recommended when theophylline, warfarin, and digoxin are co-administered with cethromycin.

5.4 Dose-Response Relationship / Clinical Dose Selection

In animal infections models, pharmacodynamic parameters C_{max}/MIC and AUC/MIC were identified as best predictive of cethromycin efficacy. Free (*f*) plasma exposures of fC_{max}/MIC = 1 and *f*AUC/MIC = 50 were associated with bacteriostatic effects in a neutropenic murine pneumonia model with *Streptococcus pneumoniae*. When a 4.4% free fraction is assumed and the MIC_{90} (0.03 μg/mL) for *S. pneumoniae* from pivotal Phase 3 trials is applied, fC_{max}/MIC and *f*AUC/MIC ratios for 300 mg QD are 1.5 and

9.5, respectively. However, it should be noted that intrapulmonary penetration of cethromycin in animals is unknown and presumed to be less than that of humans.

The proposed clinical dose of cethromycin for the treatment of mild and moderate community-acquired pneumonia (CAP) is 300 mg QD for 7 days. A range of doses was tested in Phase 2 CAP trials, one which evaluated 150 mg QD versus 150 mg BID for 10 days, and another which evaluated 300 mg QD versus 600 mg QD for 7 days. Although a lower dosing regimen of 150 mg QD appeared to be effective for the treatment duration of 10 days, results support the proposed regimen of 300 mg QD for 7 days. No additional efficacy was gained, and only an increased incidence of adverse events was observed with doses greater than 300 mg QD.

No exposure-response relationship was evaluated in patients with mild or moderate CAP.

5.5 Cardiac Repolarization
In a thorough QT clinical study of 238 healthy subjects, multiple doses of cethromycin 300 mg QD for 5 days had no effect on the QTc interval. Following multiple doses of 900 mg QD for 5 days (5-fold higher C_{max}), the maximum mean increase in QTc from placebo was 9.0 ms (95% CI, 12.2 ms).

VI. EFFICACY

Overview of Pivotal Studies for CABP
Two studies were conducted by Advanced Life Sciences, Inc. to support a claim for treatment of mild-to-moderate community-acquired bacterial pneumonia. These studies were active-controlled, double-blind, parallel group, multi-center non-inferiority studies of patients with mild-to-moderate CABP, studies CL05-001 and CL06-001. Both studies were identical in design. Patients were randomly assigned in a 1:1 ratio to receive cethromycin (300 mg daily for 7 days) or clarithromycin (250 mg twice daily for 7 days). Study CL05 was conducted at 62 sites in the United States, Canada, and South Africa. Study CL06 was conducted at 72 sites in Latin America, Europe, and Israel.

Adult patients with recent onset of symptoms consistent with CABP were enrolled if they had a chest X-ray consistent with CABP and at least 2 of the following signs/symptoms:

- Cough;
- Fever (oral temperature >38°C or >100.4°F, or equivalent tympanic/rectal temperature);
- Development of, or increase in, dyspnea or tachypnea (resp. rate ≥ 20/min.);
- Auscultatory findings of rales and/or evidence of pulmonary consolidation (dullness on percussion, bronchial breath sounds [crackles, rhonchi, wheezes, or egophony]);

- Elevated peripheral white blood cell count (WBC > 10,000/mm^3); or 15% immature neutrophils; or leukopenia (WBC < 4,500/mm^3).

Patients were enrolled if they were considered suitable candidates for oral antibiotic therapy and were able to swallow capsules intact. Written voluntary informed consent was also required for inclusion. Patients were required to have samples collected for microbiological testing within 48 hours prior to enrollment:

- Mucopurulent or purulent respiratory/sputum sample for Gram stain, culture and susceptibility testing;
- Blood samples for culture of typical aerobic microorganisms (aerobic bottle only x2 samples) and serology for atypical pathogens (*L. pneumophila*, *M. pneumoniae*, and *C. pneumoniae*);
- Urine sample for antigen detection of *L. pneumophila*.

The following were exclusion criteria for the trials:

- Hospitalization in the previous 4 weeks or residence at a chronic care facility;
- Active tuberculosis, empyema, lung abscess, pulmonary embolism, pulmonary edema, cystic fibrosis, lung tumor, bronchial obstruction, history of post-obstructive pneumonia (COPD was not a reason for exclusion), or known/suspected *Pneumocystis carinii* pneumonia;
- Treatment with a long-acting injectable antimicrobial (e.g., benzathine penicillin) within 4 weeks, treatment with ceftriaxone, azithromycin, or dirithromycin within 7 days, or >24 hour of treatment with other antibiotics within 7 days prior to study drug administration. Treatment with one dose of a short-acting antibiotic was allowed;
- Any infection requiring use of concomitant antimicrobial agents, in addition to study drug;
- Hypersensitivity or allergic reactions to macrolide, ketolide, quinolone, azalide or streptogramin antimicrobials;
- Treatment with an investigational drug within 4 weeks prior to study drug administration;
- Pregnant or lactating females;
- Known significant renal or hepatic impairment indicated by recent chemistries (serum creatinine ≥ 2 mg/dL, AST > 2x ULN, ALT > 2x ULN, GGT >2x ULN, total bilirubin ≥ 1.5x ULN);
- History of impaired renal function (creatinine clearance < 50 mL/min);
- Uncontrolled clinically significant cardiovascular, pulmonary, metabolic, gastrointestinal, neurological or endocrine disease, malignancy, or other abnormality (other than the disease being studied);
- Patients who required parenteral antimicrobial therapy for treatment of pneumonia;

- Underlying condition or disease state that would interfere with completion of study procedures and evaluations or absorption of study drug.
- Receiving or likely to require the following drugs prior to or during study drug treatment:
    - astemizole, or pimozide,
    - theophylline, carbamazepine, dexamethasone, phenobarbital, phenytoin, St. John's wort, lamotrigine, troglitazone, warfarin, and digitalis glycoside (other barbiturates could be used with careful monitoring)
    - midazolam, triazolam, and laprazolam, unless the subject was carefully monitored
    - simvastin, lovastatin and atorvastatin (These patients could be enrolled if these medications were stopped at the baseline visit. The medications could be restarted 32 hours after the last dose of study drug.)
- Currently receiving or likely to need any of the following medications during the study:
    - other systemic antimicrobial therapy
    - rifampin or rifabutin
- Immunocompromised patients (neutropenia with granulocytes $\leq 1000/mm^3$), patients receiving immunosuppressive agents, or patients with known HIV infection and an AIDS defining condition or CD4 count $< 200/mm^3$;
- Known or suspected central nervous system disorder that could predispose to seizures or lower the seizure threshold;
- Prior treatment with cethromycin in this study or another study;
- Patients with signs of septic shock (systemic inflammatory response syndrome) such as mental confusion, severe hypoxemia requiring supplemental oxygen or mechanical ventilation, hypotension requiring fluid resuscitation or pressors, or other condition requiring intensive care unit admission.

Patients were evaluated at baseline, 4-6 days after initiation of study drug, 24-72 hours after the last dose, and 7-14 days after the last dose of study medication – the test-of-cure (TOC) visit. There was also a telephone call for follow-up at 30-33 days after the last dose of study drug.

The primary efficacy endpoint for the studies was the clinical cure rate at the TOC visit. Clinical cure at the TOC visit was defined as improvement or return to pre-infection state or lack of progression in all pulmonary infiltrates originally consistent with pneumonia on chest radiograph, AND resolution of all signs and symptoms of CAP originally present at the time of enrollment.

Patients could be considered clinical failures at any study visit under the following conditions:

- Persistence or worsening in signs or symptoms of the acute process after 3-5 days of therapy or requirement for additional antibiotic for initial pneumonia due to lack of improvement;
- Development of new pulmonary infection or extrapulmonary infection requiring antimicrobial therapy other than, or in addition to, the study medication;
- Progression of chest radiological abnormalities;
- Death due to pneumonia.

An indeterminate response at the TOC visit was defined as "The evaluation was not possible (e.g., lost to follow-up, disallowed medication use, premature discontinuation due to an adverse event, intercurrent illness, or major protocol violation)". The reason for indeterminate response was to be recorded on the case report form.

The study populations were defined as follows:

Safety Population – All patients who received at least one dose of study medication and had at least one post-baseline assessment

Intent-to-Treat Population – All patients who received at least one dose of study medication and had a clinical diagnosis consistent with bacterial pneumonia, confirmed by a positive pre-treatment X-ray and at least two of the signs/symptoms in the inclusion criteria

Clinically Evaluable Population – Conditions for inclusion in this population were:

- A minimum duration of therapy of 3 days of study medication was required; 80% of prescribed study medication was taken for patients to be considered clinical cures
- The clinical diagnosis of pneumonia was supported by a positive chest X-ray and appropriate clinical signs/symptoms
- No other systemic antimicrobial agent was administered during the period from 2 weeks prior to the start of study drug until the TOC evaluation, unless the subject was considered a study treatment failure or had an intercurrent illness and was indeterminate

Bacteriologically Evaluable Population – In addition to the criteria above for clinical evaluability, at least one specific pathogen was isolated with significant growth from a baseline culture or identified via serology or antigen testing

The ITT and CE population were considered co-primary populations for the evaluation of efficacy. The protocols stated that the non-inferiority (Delta) margin to be applied would be based on the cure rate as follows:

Highest cure rate:	Delta:
Greater than or equal to 90%	-10%
Greater than or equal to 80% and less than 90%	-15%
Greater than or equal to 70% and less than 80%	-20%

The sample size was determined to be approximately 500 patients per study. Assuming 90% clinical cure rates in the clinically evaluable population, and 80% clinical evaluability, 250 subjects overall would provide 90% power to assure that the lower limit of the two-sided 95% CI for the difference (cethromycin-clarithromycin) between treatment groups would be greater than 10%.

Patient Demographics

In study CL05, 292 patients were randomized to each treatment group. One patient in each group never received study drug, leaving 291 patients per arm in the safety population. In the cethromycin group, thirty patients were excluded from the ITT population for insufficient radiographic evidence of pneumonia, or confounding disease. In the clarithromycin group, there were 37 patients excluded from the ITT population for the same reasons.

In study CL06, 261 patients were randomized to each treatment group. One patient in the clarithromycin arm never received study medication. Four cethromycin patients and seven clarithromycin patients were excluded from the ITT analysis for insufficient radiographic evidence of pneumonia or confounding disease. The table below shows the number of patients in each of the treatment groups for both studies.

Table 6.1: Patient Disposition

Analysis Population	Study CL05			Study CL06		
	Cethromycin N (%)	Clarithromycin N (%)	Total N (%)	Cethromycin N (%)	Clarithromycin N (%)	Total N (%)
ITT	261 (100)	254 (100)	515 (100)	257 (100)	253 (100)	510 (100)
Clinically Evaluable	218 (83.5)	208 (81.9)	426 (82.7)	224 (87.2)	221 (87.4)	445 (87.3)
Bacteriologically Evaluable	73 (28)	69 (27.2)	142 (27.6)	64 (24.9)	63 (24.9)	127 (24.9)

Table 6.3 provides demographic information for patients in the ITT population by treatment group for both pneumonia studies. The demographic data for ITT patients is comparable across treatment arms for both studies. There were some differences in race and ethnicity across the two studies, consistent with the geographic regions in which the studies were conducted.

Baseline clinical characteristics are not shown here, but were comparable across treatment groups in both clinical studies. Almost all patients were reported to have cough

and sputum production. For study CL05, tachypnea was reported in approximately 60% of patients, dyspnea in over 90%, and fever in 39%. For study CL06, tachypnea was reported in approximately 65% of patients, dyspnea in about 62%, and fever in about 65%. Of note with regard to baseline characteristics, approximately 50% of ITT patients in the two pneumonia studies had a PORT score of 1. This will be discussed further with the FDA sensitivity analyses.

Table 6.2: ITT Patient Demographics

Characteristic Category	Study CL05		Study CL06	
	Cethromycin (n=261) # (%)	Clarithromycin (n=254) # (%)	Cethromycin (n=257) # (%)	Clarithromycin (n=253) # (%)
Gender				
Female	128 (49)	128 (50.4)	103 (46)	110 (49.8)
Male	133 (51)	126 (49.6)	121 (54)	111 (50.2)
Race				
White	210 (80.5)	199 (78.3)	239 (93.0)	234 (92.5)
Black	31 (11.9)	27 (10.6)	1 (0.4)	1 (0.4)
Asian	12 (4.6)	17 (6.7)	1 (0.4)	0
Other	8 (3.1)	11 (4.3)	16 (6.2)	18 (7.1)
Ethnicity				
Hispanic	15 (5.7)	11 (4.3)	87 (33.9)	90 (33.5)
Non-hispanic	246 (94.3)	243 (95.7)	170 (66.1)	163 (64.4)
Alcohol Use				
Non-Drinker	129 (49.4)	116 (45.7)	160 (62.3)	169 (66.8)
Drinker	119 (45.6)	125 (49.2)	93 (36.2)	78 (30.8)
Other	13 (5.0)	13 (5.1)	4 (1.6)	6 (2.4)
Tobacco Use				
Never Used	117 (44.8)	133 (44.5)	131 (51.0)	141 (55.7)
User	89 (34.1)	95 (37.4)	84 (32.7)	66 (26.1)
Ex-User	55 (21.1)	46 (18.1)	42 (16.3)	46 (18.2)
Characteristic Statistic				
Age Mean (Median)	48.8 (47.0)	50.5 (51.0)	47.8 (48.0)	46.4 (47.0)
Weight (kg) Mean (Median)	81.1 (80.0)	80.3 (77.1)	74.8 (70.0)	73.1 (71.0)

Study Outcomes

The primary efficacy endpoint for the pneumonia trials was clinical cure rate at the test-of-cure visit. This outcome was evaluated in the co-primary analysis populations, the ITT and clinically evaluable patient groups. Table 6.3 shows the clinical cure rates at the TOC visit for both pneumonia studies in the co-primary analysis populations. The 95% confidence intervals (CI) differ slightly from those provided by the NDA applicant.

Estimation of 95% confidence limits for the treatment difference in clinical cure rates (cethromycin – clarithromycin) at the test of cure visit were performed using normal approximation to the binomial distribution with a continuity correction of $(1/n_1 + 1/n_2)^{-1}$. Since normal approximation methods may not be valid in estimating 95% confidence limits in samples with high cure rates (p) or limited sample size (n), exact binomial 95% confidence intervals were computed in cases with $np(1-p) < 5$ in one or more comparison groups. The 95% confidence intervals computed in secondary and other FDA analyses followed the same approach as described for the primary analysis, however confidence intervals were not computed in cases with $n < 10$ in either sample.

In Study CL05, cure rates in the ITT population were 83.1% in cethromycin patients and 81.1% in clarithromycin patients, with a treatment difference of 2% and a 95% CI of (-5, 9). Cure rates in the CE population were 94% for cethromycin patients and 93.8% for clarithromycin patients with a treatment difference of 0.3% and 95% CI of (-4.7, 5.3). These study CL05 results showed comparable cure rates for cethromycin and clarithromycin in the primary analysis populations.

In study CL06, cure rates in the ITT population were 82.9% in cethromycin patients and 88.5% in clarithromycin patients, with a treatment difference of -5.7% and a 95% CI around the difference of (-12.1, 0.8). Cure rates in the CE population were 91.5% for cethromycin patients and 95.9% for clarithromycin patients with a treatment difference of -4.4% and 95% CI of (-9.3, 0.5). The cure rates for cethromycin patients were lower than for clarithromycin patients in this study, resulting in more negative lower bounds for the 95% CI.

Table 6.3: Primary Outcome Analyses

Analysis Population	Cethromycin cure/N (%)	Clarithromycin cure/N (%)	Treatment Difference, (95% CI) [a]
Study CL05			
ITT (n=515)	217/261 (83.1)	206/254 (81.1)	2.0 (-5.0, 9.0)
CE (n=426)	205/218 (94.0)	195/208 (93.8)	0.3 (-4.7, 5.3)
Study CL06			
ITT (n=510)	213/257 (82.9)	224/253 (88.5)	-5.7 (-12.1, 0.8)
CE (n=445)	205/224 (91.5)	212/221 (95.9)	-4.4 (-9.3, 0.5)

a – 95% CIs computed using normal approximation for the binomial distribution with continuity correction. Exact tests performed in cases where $np(1-p) < 5$ for either sample.

The NDA applicant provided information on clinical outcomes for patients with bacterial pathogens identified at baseline. Table 6.4 provides the clinical cure rates for patients with the listed pathogens in the ITT and bacteriologically evaluable (BE) populations for

both studies. It should be noted that the number of patients with documented *S. pneumoniae* infection at baseline is low for both studies. It is also notable that the numbers of patients with documented *H. influenzae* or *S. aureus* infections are similar to the *S. pneumoniae* infection numbers. The point estimates for cure rates by pathogen in cethromycin patients are comparable to those for clarithromycin patients, with the exception of *H. influenzae* in Study CL06. Cure rates for cethromycin patients with *H. influenzae* at baseline were lower than the cure rates for clarithromycin patients; however, the *H. influenzae* cure rates in Study CL05 did not show the same finding.

Table 6.4: Clinical Cure Rate by Baseline Pathogen

Baseline Pathogen	Cethromycin Cure/N (%)	Clarithromycin Cure/N (%)	Cethromycin Cure/N (%)	Clarithromycin Cure/N (%)
ITT Population	**Study CL05**		**Study CL06**	
H. influenzae	33/36 (92%)	23/26 (88%)	24/33 (73%)	21/22 (95%)
S. pneumoniae	10/12 (83%)	17/22 (77%)	15/19 (79%)	7/11 (64%)
M. catarrhalis	3/3	6/6	2/4	3/4
S. aureus	10/14 (71%)	13/14 (93%)	7/8 (88%)	9/11 (82%)
L. pneumophila	4/4	3/5	1/1	4/4
BE Population	**Study CL05**		**Study CL06**	
H. influenzae	33/35 (94%)	20/20 (100%)	23/27 (85%)	21/22 (95%)
S. pneumoniae	9/9 (100%)	15/18 (83%)	15/17 (88%)	7/9 (78%)
M. catarrhalis	2/2	6/6	2/3	3/4
S. aureus	9/10 (90%)	13/13 (100%)	6/7 (86%)	9/9 (100%)
L. pneumophila	4/4	3/3	0	4/4

The NDA applicant also reported outcomes for patients with *Mycoplasma pneumoniae* and *Chlamydophila (Chlamydia) pneumoniae* infections as determined by serology. In the ITT population of Study CL05, cure rates for M. pneumoniae were 11/11 for cethromycin and 17/18 (94%) for clarithromycin; cure rates for C. pneumoniae were 6/6 for cethromycin and 5/7 (71%) for clarithromycin. In Study CL06 ITT population, there were six patients in each treatment group with *C. pneumoniae* by serology, all were considered cured. For *M. pneumoniae* in the ITT population of Study CL06, cure rates were 19/20 (95%) for cethromycin patients and 20/23 (87%) for clarithromycin patients.

FDA Sensitivity Analysis

The FDA reviewers conducted sensitivity analyses that excluded patients from the primary analysis based on any one of the following factors:

- Patients with PORT score = 1
- Patients with prior antibiotic use
- Patients with atypical pathogens as the sole pathogen identified

The purpose of this analysis was to identify patient populations in the two studies for whom there is a reasonable basis to apply the non-inferiority margins, based on historical

evidence of the treatment effect of antibiotics in pneumonia. Patients with a PORT score of 1 accounted for approximately 48% of patients in Study CL05 and 50% of patients in Study CL06. These patients were excluded from the FDA analysis because of the uncertainty of the treatment effect of antibiotics in these patients at low risk of mortality.

Patients with antibiotic use just prior to the start of study drug were excluded from the FDA analysis, because recent data have demonstrated that prior treatment with antibiotics effective against *S. pneumoniae* can affect clinical outcomes[1]. There were 63 patients in Study CL05 and 60 patients in CL06 who received antibiotics prior to start of study drug. Antibiotic information was reviewed for each of these patients. Two patients in study CL05 received topical treatments (tetracycline for acne and valacyclovir for cold sores) that would not affect outcome. One patient in Study CL06 received co-trimoxazole 14 days prior to the study drug treatment, unlikely to affect treatment. The other 61 patients in Study CL05 and 59 patients in Study CL06 received antibiotics active against *S. pneumoniae* just prior to study drug treatment, and were excluded from the FDA analysis.

Patients with atypical pathogens identified as the sole pathogen were also excluded from the FDA sensitivity analysis. The laboratory and microbiological data for each patient were reviewed to ensure that patients with typical bacterial pathogens would not be excluded. There were 47 patients in Study CL05 and 55 patients in Study CL06 that could be excluded on this basis.

Table 6.5 shows the results for the primary endpoint analysis once the patients identified above were excluded. As expected, the smaller number of patients in the FDA sensitivity analyses resulted in wider 95% confidence intervals. In the Study CL05 ITT population, the cure rates were 80.9% for cethromycin patients and 78.5% for clarithromycin patients. The treatment difference and 95% CI were 2.4% (-8.8, 13.6). The point estimates and treatment differences in the Study CL05 sensitivity analyses are fairly consistent with the sponsor's overall results. In the Study CL06 ITT population, the cure rates were 76.1% for cethromycin patients and 85.7% for clarithromycin patients. The treatment difference was -9.6%, and the 95% CI was (-20.9, 1.6). In Study CL06, the treatment difference widens in both the ITT and CE populations, because of lower cure rates in the cethromycin arm than for the overall population.

[1] Pertel PE, et al "Effects of Prior Effective Therapy on the Efficacy of Daptomycin and Ceftriaxone for the Treatment of Community-Acquired Pneumonia" *Clin. Infect. Dis.* 46(8):1152-6, April 15 2008

Table 6.5: FDA Sensitivity Analysis – Primary Endpoint

Analysis Population	Cethromycin cure/N (%)	Clarithromycin cure/N (%)	Treatment Difference, (95% CI) [a]
Study CL05			
ITT (n=515)	89/110 (80.9)	95/121 (78.5)	2.4 (-8.8, 13.6)
CE (n=426)	84/89 (94.4)	89/93 (95.7)	-1.3 (-8.7, 6.1)
Study CL06			
ITT (n=510)	86/113 (76.1)	90/105 (85.7)	-9.6 (-20.9, 1.6)
CE (n=445)	85/98 (86.7)	86/92 (93.5)	-6.7 (-16.2, 2.7)

a – 95% CIs computed using normal approximation for the binomial distribution with continuity correction. Exact tests performed in cases where np(1-p) < 5 for either sample.

Table 6.6 shows the cure rates by baseline pathogen in the ITT and bacteriologically evaluable populations of both studies using the FDA-defined population. It should be noted that the proportion of the population with documented bacterial infection is small.

Table 6.6: FDA Sensitivity Analysis – Cure Rates by Pathogen

Population/ Pathogen	Cethromycin Cure/N (%)	Clarithromycin Cure/N (%)	Cethromycin Cure/N (%)	Clarithromycin Cure/N (%)
ITT	**Study CL05**		**Study CL06**	
H. Influenzae	14/16 (88)	14/16 (88)	7/13 (54)	12/13 (93)
S.pneumoniae	8/9 (89)	11/14 (79)	6/9 (67)	4/8 (50)
M.catarrhalis	3/3 (100)	5/5 (100)	1/3 (33)	3/4 (75)
S.aureus	4/5 (80)	6/7 (86)	1/2 (50)	1/2 (50)
BE	**Study CL05**		**Study CL06**	
H. Influenzae	14/15 (93)	11/11 (100)	7/11 (64)	12/13 (93)
S.pneumoniae	7/7 (100)	10/11 (91)	6/7 (86)	4/6 (67)
M.catarrhalis	2/2 (100)	5/5 (100)	1/2 (50)	3/4 (75)
S.aureus	3/3 (100)	6/6 (100)	1/2 (50)	1/1 (100)

VII. SAFETY

Exposure to Study Drugs

A total of 5095 subjects received at least 1 dose of cethromycin in the Phase 1, 2, and 3 studies that were integrated across the cethromycin clinical program. Of these, 6 subjects had no post-baseline assessments and were excluded from the safety population. Thus,

5089 subjects received at least 1 dose of cethromycin in the Phase 1, 2, and 3 studies, had at least 1 post-baseline safety assessment, and have been included in the safety population for analysis.

Of all cethromycin-treated subjects in the Phase 1, 2, and 3 studies combined included in the safety population, 2195 received a total daily dose (TDD) of 300 mg, administered as 100 mg TID, 150 mg BID, or 300 mg QD. A total of 1375 subjects received cethromycin 300 mg QD, the dose for which approval is sought, and 1863 received cethromycin ≥300 mg QD, which included doses of 300 mg QD, 600 mg QD, 800 mg QD, 900 mg QD, and 1200 mg QD. In addition, 230 subjects received placebo in the Phase I studies and 1721 subjects received active controls in the Phase 1, 2, and 3 studies that included clarithromycin, moxifloxacin, azithromycin, levofloxacin, and penicillin V.
Total daily doses of cethromycin <300 mg were received by 2219 subjects and doses of >300 mg were received by 757 subjects.

Among all cethromycin-treated subjects in the Phase 1, 2, and 3 studies combined, the majority completed study participation (89.3%).

A total of 552 subjects received at least 1 dose of cethromycin 300 mg QD and 551 received at least 1 dose of clarithromycin 250 mg BID in the 2 Phase 3 controlled CAP studies that were integrated. Of these, 4 cethromycin subjects and 3 clarithromycin subjects had no post-baseline assessments and were excluded from the safety population. Thus, 548 subjects in each treatment group received at least 1 dose of study drug in the 2 Phase 3 controlled CAP studies, had at least 1 post-baseline safety assessment, and have been included in the safety population for analysis.

Among subjects who received cethromycin 300 mg QD in the 2 Phase 3 controlled CAP studies combined, total drug exposure ranged from 300 mg to 2100 mg, with a mean total dose of 2048 mg. The majority of the cethromycin subjects received treatment for ≥6 days (95.8%).

Discontinuations
Across the entire cethromycin clinical program, a total of 137 subjects who received cethromycin, 55 subjects who received active controls, and 1 subject who received placebo experienced treatment-emergent adverse events resulting in discontinuation.

In the 2 Phase 3 controlled CAP studies combined, the overall incidence of treatment-emergent adverse events resulting in discontinuation was similar between subjects who received cethromycin 300 mg QD (2.4%) or clarithromycin 250 mg BID (3.6%). The most common treatment-emergent adverse events resulting in discontinuation in both treatment groups were associated with gastrointestinal disorders (cethromycin: 0.9%; clarithromycin: 1.1%) and infections and infestations (cethromycin: 0.7%; clarithromycin: 1.3%). The only specific treatment-emergent adverse events resulting in discontinuation reported by more than 1 subject in the cethromycin group were pneumonia (0.7%), abdominal pain (0.5%), nausea (0.4%), and vomiting (0.4%). In the

clarithromycin group, the only specific treatment-emergent adverse events resulting in discontinuation reported by more than 1 subject were diarrhea (0.5%), nausea (0.4%), pneumonia (0.4%), and lobar pneumonia (0.4%). The majority of the treatment-emergent adverse events resulting in discontinuation were considered by the investigator to be mild or moderate in intensity.

Summary of Clinical Safety
The following overview summarizes the key safety findings of the Summary of Clinical Safety.

Common Adverse Events
Evaluation of treatment-emergent adverse events across the cethromycin clinical program revealed no unexpected safety concerns. Dysgeusia (metallic aftertaste) was the most prominent effect noted with cethromycin dosing. As is typically noted with antibacterial agents, gastrointestinal events were also commonly observed with cethromycin administration.

Among the 1253 subjects who received at least 1 dose of cethromycin in the Phase 1 studies, treatment-emergent adverse events that occurred in 5% or more of all cethromycin-treated subjects included dysgeusia (22.7%), headache (14.4%), nausea (13.7%), diarrhea (8.5%), and dizziness (7.3%). A notably higher incidence of dysgeusia, nausea, and diarrhea occurred in all cethromycin-treated subjects (22.7%, 13.7%, and 8.5%, respectively) compared with subjects who received placebo (2.6%, 1.3%, and 3.9%, respectively). In addition, a notably higher incidence of nausea, diarrhea, and vomiting occurred in all cethromycin-treated subjects (13.7%, 8.5%, and 4.2%, respectively) compared with subjects who received active controls (6.4%, 1.8%, and 0%, respectively).

Among the 3836 cethromycin-treated subjects and 1611 subjects who received active controls in all Phase 2/3 studies combined, treatment-emergent adverse events that occurred in 5% or more of all cethromycin-treated subjects included dysgeusia (7.5%), diarrhea (7.3%), nausea (6.6%), and headache (5.3%). The only notable difference observed between all cethromycin-treated subjects and subjects who received active controls was a higher incidence of dysgeusia in all cethromycin-treated subjects (7.5%) compared with subjects who received active controls (2.2%). Among the 870 subjects who received cethromycin 300 mg QD, treatment-emergent adverse events that occurred in 5% or more of subjects who received cethromycin 300 mg QD in the Phase 2/3 studies combined included dysgeusia (12.2%), diarrhea (6.9%), and nausea (6.7%). The incidence of dysgeusia tended to be higher in subjects who received cethromycin 300 mg QD compared with all cethromycin-treated subjects, while the incidences of other specific treatment-emergent adverse events were similar between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD.

The overall incidence of treatment-emergent adverse events was similar among subjects who received total daily cethromycin doses of <300 mg (45.9%) and 300 mg (TDD:

46.3%; QD: 48.3%), with a higher incidence noted among subjects who received >300 mg (62.3%). The incidences of gastrointestinal disorders and dysgeusia increased with increasing dose. When analyzed by regimen, the overall incidence of treatment-emergent adverse events was lower with the cethromycin 100 mg TID regimen (23.8%) compared with the 150 mg BID (47.1%) and 300 mg QD (48.3%) regimens. In addition, the incidence of dysgeusia was notably higher with QD dosing (12.2%) compared to BID (5.5%) or TID (4.8%) dosing.

Among the 548 subjects who received cethromycin 300 mg QD and 548 subjects who received clarithromycin 250 mg BID in the 2 Phase 3 controlled CAP studies combined, the most common treatment-emergent adverse events experienced in both treatment groups were dysgeusia (9.3% and 4.0%, respectively), diarrhea (4.7% and 4.4%, respectively), nausea (3.6% and 2.4%, respectively), and headache (2.7% and 4.2%, respectively). A statistically significantly higher incidence of dysgeusia was observed in cethromycin subjects compared with clarithromycin subjects (9.3% vs. 4.0%); while a statistically significantly higher incidence of urinary tract infection was observed in clarithromycin subjects compared with cethromycin subjects (1.3% vs. 0%).

Deaths
Across the cethromycin clinical program, a total of 4 subjects who received cethromycin and 6 subjects who received active controls died due to adverse events that began after the start of study drug therapy or within 30 days after the end of study drug therapy. In addition, 1 cethromycin subject died from acute renal failure that started prior to beginning therapy and 1 active control subject died 50 days after completing study drug. All of the deaths occurred in Phase 2/3 studies of CAP or bronchitis. In the Phase 3 studies, there were 2 and 4 deaths in patients receiving cethromycin and clarithromycin, respectively. Of note, 4 out of 12 total deaths in the program were in studies conducted in South Africa, and 2 of those were from the same study site.

Per the applicant, none of the adverse events that led to death were considered related to study drug. In contrast, per the FDA reviewer, there were 2 deaths in the Phase 3 studies (one in each treatment arm), and 1 death in the phase 2 study (cethromycin arm) which were *possibly related* to study drug therapy. All subjects who died in the cethromycin clinical program are listed by study and treatment group in Table 7.1 below:

Table 7.1: Patient Deaths in All Phase 2, 3 Studies

Study #	Subject	Age/ Sex	Adverse Event	Total Days on Therapy	Days Post-Therapy to Death	Relationship of AE to study medication (investigator/FDA assessment)
Phase 2/3 Studies: Cethromycin						
CL05-001	3006-0089	58/M	AMI	6	0	**Not Related/Possibly Related**
CL06-001	5606-0001	52/M	Small Cell Lung Cancer, Hemoptysis	8	14	Not Related/Not Related
M00-217	17454-21391	76/M	Acute Renal Failure	3	1	Not Related/Not Related
M00-219	18387-34086	65/M	Cyanosis, Confusion, Disorientation, Coronary Thrombosis	3	1	**Not Related/Possibly Related**
	18493-34045	40/M	Pneumonia	4	8	Not Related/Not Related
Phase 2/3 Studies: Active Controls						
CL05-001 Clari	2011-0036	66/F	Squamous Lung Cell Carcinoma, Arrhythmia, Cardiac Arrest	7	52	Not Related/Not Related
	3004-0013	59/M	Pneumonia	5	0	**Probably Not Related/Possibly Related**
	3006-0056	79/F	AMI	4	1	Not Related/Not Related
CL06-001 Clari	5704-0001	71/M	Lung Carcinoma	4	14	Not Related/Not Related
M00-216 Azith	9773-20780	64/M	COPD	1	17	Not Related/Not Related
	9625-20933	81/F	Muscle Hemorrhage	3	11	Not Related/Not Related
M00-217 Levo	17677-21188	87/F	AMI	4	19	Not Related/Not Related

QD=once daily; BID=twice daily; M=male; F=female; Azith=azithromycin; Levo=levofloxacin; Clari=Clarithromycin; AMI=acute myocardial infarction; COPD=chronic obstructive pulmonary disease

Reviewer's Summary:

Overall in the combined Phase 3 studies, there were 2 deaths in the cethromycin treatment group, or 0.004%, and 4 deaths in the clarithromycin treatment group, or 0.007%. No notable differences were observed with respect to the types of events that led

to death among the two treatment groups, although lung cancer accounted for 1 of the deaths in the cethromycin group and 2 of the deaths in the clarithromycin group.

Across all Phase 2 and 3 studies combined, there were 2 deaths in the cethromycin group that were possibly related to study drug, and 1 death in the control group that was possibly related to study drug. In both groups, it appeared that these deaths were the result of treatment failure.
There were no notable differences observed with respect to the types of events that led to death among the cethromycin or active control subjects.
There was no imbalance between the two treatment groups in the rate of deaths, or in cause of death in the Phase 3 studies. However, the numbers are small (the study is not powered to assess deaths as an end-point), and preclude from making definitive conclusions.

Nonfatal Serious Adverse Events
In the 2 Phase 3 controlled CAP studies combined, the overall incidence of treatment-emergent serious adverse events was similar between subjects who received cethromycin 300 mg QD (4.6%) or clarithromycin 250 mg BID (3.3%). No statistically significant differences were observed between the treatment groups for the overall incidence of treatment-emergent serious adverse events (p-value = 0.351) or for the incidence of any system organ class or preferred term. The majority of the treatment-emergent serious adverse events reported were considered by the investigator to be moderate or severe in intensity and none were considered related to study drug. The following table summarizes these events by system organ class:

Table 7.2: SAE by System Organ Class (SOC)

MedDRA SOC	Cethromcyin (n=548)	Clarithromycin (n=548)
Cardiac disorders	4 (0.7%)	2 (0.4%)
Gastrointestinal disorders	2 (0.4%)	0 (0%)
Immune System disorders	1 (0.2%)	0 (0%)
Infections and Infestations	9 (1.6%)	10 (1.8%)
Injury, poisoning, procedural complications	1 (0.2%)	0 (0%)
Investigations	1 (0.2%)	0 (0%)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	4 (0.7%)	4 (0.7%)
Renal and urinary disorders	1 (0.2%)	0 (0%)
Respiratory, thoracic, and mediastinal disorders	7 (1.3%)	3 (0.5%)
Total SAEs	25 (4.6%)	18 (3.3%)

Notes: Subjects experiencing multiple SAE within the same SOC are counted only one for that same SOC. Percentages are based on the total number of safety-eligible subjects within the treatment/dose group.

Overall, the balance between both arms was even with regard to all SAEs reported. The most common SAE by SOC in both arms was infections and infestations. The majority of these events were secondary complications such as pneumonia, appendicitis, empyema, lung abscess, lobar pneumonia, otitis media, pulmonary tuberculosis.

No specific SAE preferred term was reported in a patient more than once per group, except for pneumonia (6 in the cethromycin group, and 4 in the clarithromycin group, which also had 3 patients with lobar pneumonia), that was balanced between the two groups. Patients in the cethromycin arm had a higher percentage of respiratory, thoracic, and mediastinal disorders than the clarithromycin arm, but this was not statistically significant. The preferred terms in this category were asthmatic crisis, bronchospasm, chronic obstructive pulmonary disease, paroxysmal nocturnal dyspnea, hemoptysis, pleural effusion, pulmonary edema, and pneumothorax.

Special Adverse Events

Analysis of Adverse Events by Organ System or Syndrome
Given the observed effects of another ketolide agent, particular attention was given to the analyses of topics of special interest including safety data relevant to hepatotoxicity, visual disturbances, loss of consciousness, and exacerbation of myasthenia gravis.

Hepatotoxicity
The potential for hepatotoxicity with cethromycin was assessed by a review of treatment-emergent and drug-related, treatment-emergent adverse events potentially associated with hepatotoxicity and shifts from normal baseline values to ≥3 × ULN and ≥5 × ULN in post-baseline hepatic function values of ALT, AST, alkaline phosphatase, GGT, and total bilirubin. In all Phase 1 studies combined, the percent of subjects who experienced at least 1 treatment-emergent adverse event potentially associated with hepatotoxicity was 1.1% for cethromycin; none of the subjects who received placebo or active controls experienced these types of events. In all Phase 2/3 studies, the incidence of at least 1 treatment-emergent adverse event potentially associated with hepatotoxicity was similar between subjects who received cethromycin (2.8%) and those who received active controls (2.4%). There was no consistent pattern of higher percentages of subjects in the cethromycin versus active control group shifting from normal baseline to ≥3 × ULN and ≥5 × ULN following treatment. No subject met the criteria for Hy's Law, a predictor of liver toxicity. Hy's Law cases have the following three components:

1. The drug causes hepatocellular injury, generally shown by more frequent 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control agent or placebo.

2. Among subjects showing such AT elevations, often with ATs much greater than 3xULN, some subjects also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (serum alkaline phosphatase (ALP) activity >2xULN).

3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C, preexisting or acute liver disease, or another drug capable of causing the observed injury.

In the 2 Phase 3 controlled CAP studies combined, the incidence of treatment-emergent adverse events potentially associated with hepatotoxicity was slightly higher for subjects who received cethromycin 300 mg QD (5.1%) compared to subjects who received clarithromycin 250 mg BID (3.5%). Among cethromycin-treated subjects, the only specific treatment-emergent adverse events potentially associated with hepatotoxicity experienced by ≥1% of subjects were ALT increased (1.8%), hepatic enzyme increased (1.3%), and AST increased (1.1%), which were similar to that observed in the active control group (1.5%, 0.9%, and 0.9%, respectively). A summary of treatment-emergent adverse events of special interest potentially associated with hepatotoxicity by treatment group in the 2 Phase 3 controlled CAP studies combined is presented in Table 7.3.

Table 7.3: Treatment-Emergent Adverse Events Associated with Hepatotoxicity by Treatment Group (All Phase 3 Controlled CAP Studies)

Search Criteria Preferred Term	**Cethromycin 300 mg QD (N=548)**	**Clarithromycin 250 mg BID (N=548)**
Subjects with at least 1 TEAE potentially associated with hepatotoxicity	28 (5.1)	19 (3.5)
ALT Increased	10 (1.8)	8 (1.5)
Hepatic Enzyme Increased	7 (1.3)	5 (0.9)
AST Increased	6 (1.1)	5 (0.9)
GGT Increased	4 (0.7)	2 (0.4)
Hepatitis Toxic	3 (0.5)	0
Transaminases Increased	2 (0.4)	1 (0.2)
Cholelithiasis	1 (0.2)	0
Hepatitis Viral	1 (0.2)	0
Hepatic Function Abnormal	0	1 (0.2)
Hepatitis C	0	1 (0.2)
Hepatitis Cholestatic	0	1 (0.2)
Liver Function Test Abnormal	0	1 (0.2)
Portal Hypertension	0	1 (0.2)

mg=milligrams; QD=once daily; BID=twice daily; TEAE=treatment-emergent adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyltransferase
Note: Percentages are displayed in parentheses.
Applicant's data

Shifts from Baseline in Hepatic Function Tests

All Phase 1 Studies Combined

In the Phase 1 studies combined, the incidences of shifts from normal baseline hepatic function tests including ALT, AST, alkaline phosphatase, GGT, and total bilirubin to elevations ≥3 × ULN and ≥5 × ULN were all <1% among all cethromycin-treated

subjects. Among subjects with normal values at baseline, 1 placebo subject had a post-baseline ALT value ≥3 × ULN; no subjects who received active controls had post-baseline hepatic function test values ≥3 × ULN. The incidences of shifts from normal baseline to elevations in hepatic function tests ≥3 × ULN or ≥5 × ULN were similar among all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD.

Of the 5089 cethromycin-treated subjects included in the safety population for evaluation, only 1 (<0.01%) developed elevations in liver function tests that met Hy's Law (ALT or AST ≥3 × ULN and total bilirubin ≥1.5 × ULN). A short narrative is provided.

• Subject M99-142-1389-00130 was a 25-year-old male who participated in a Phase 1 study that evaluated the relationship between steady-state pharmacokinetics and the concentration of cethromycin in BAL fluid, ELF, and AC. The subject entered the study with normal liver function test values. The subject was dosed with 300 mg QD for 5 days. On Day 5 of dosing, the subject had an AST value of 165 U/L and a total bilirubin value 129.96 µmol/L; however, the laboratory noted on the chemistry report that the sample was hemolyzed, which would have affected the results. A repeat test performed approximately 6 weeks later indicated a normal AST value (23 U/L) and a slightly elevated total bilirubin value (29.07 mg/dL) that the investigator did not consider to be clinically significant.

All Phase 2/3 Studies Combined

In the Phase 2/3 studies combined, the incidences of shifts from normal baseline hepatic function tests to elevations ≥3 × ULN and ≥5 × ULN were all <1% among all cethromycin-treated subjects and subjects who received active controls. The incidences of shifts from normal baseline to elevations in hepatic function tests ≥3 × ULN or ≥5 × ULN were similar among all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD.

All Phase 3 Controlled CAP Studies Combined

In the 2 Phase 3 controlled CAP studies combined, the incidences of shifts from normal baseline in ALT, alkaline phosphatase, GGT, and total bilirubin to elevations ≥3 × ULN and ≥5 × ULN were all <1% for subjects who received cethromycin 300 mg QD; for AST, the incidence of shifts from normal baseline to elevations ≥3 × ULN was 1.1%. The incidence of shifts from normal baseline to elevations ≥3 × ULN in ALT and AST were slightly higher among subjects who received cethromycin 300 mg QD (0.9% and 1.1%, respectively) compared with subjects who received clarithromycin 250 mg BID (0.2% each). A summary of shifts from normal baseline to ≥3 × ULN and ≥5 × ULN in post-baseline hepatic function values in the 2 Phase 3 controlled CAP studies combined is presented by treatment group in Table 7.4.

Table 7.4: Shifts From Normal Baseline to >3 × ULN and >5 × ULN in Post-Baseline Hepatic Function Values by Treatment Group (All Phase 3 Controlled CAP Studies)

Variable	Cethromycin 300 mg QD (N=548)	Clarithromycin 250 mg BID (N=548)
ALT (U/L)		
≥3 × ULN	5 (0.9)	1 (0.2)
≥5 × ULN	2 (0.4)	0 (0.0)
Alkaline Phosphatase (U/L)		
≥3 × ULN	0 (0.0)	0 (0.0)
≥5 × ULN	0 (0.0)	0 (0.0)
AST (U/L)		
≥3 × ULN	6 (1.1)	1 (0.2)
≥5 × ULN	3 (0.5)	0 (0.0)
GGT (U/L)		
≥3 × ULN	1 (0.2)	0 (0.0)
≥5 × ULN	0 (0.0)	0 (0.0)
Total Bilirubin (µmol/L)		
≥3 × ULN	0 (0.0)	0 (0.0)
≥5 × ULN	0 (0.0)	0 (0.0)

mg=milligrams; QD=once daily; BID=twice daily; ULN=upper limit of normal; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyltransferase
Applicant's data

Visual Disturbances

All Phase 1 Studies Combined

In the Phase 1 studies combined, the incidence of treatment-emergent adverse events potentially associated with visual disturbances was 0.3% for all cethromycin-treated subjects; none of the subjects who received cethromycin 300 mg QD experienced these types of events. The incidence of these events was 0.9% for placebo subjects and 0% for subjects who received active controls. Each of the specific treatment-emergent adverse events potentially associated with visual disturbances was experienced by <1% of subjects and only among those who received doses >300 mg.

All Phase 2/3 Studies Combined

In the Phase 2/3 studies combined, the incidence of treatment-emergent adverse events potentially associated with visual disturbances was 0.2% for all cethromycin-treated subjects and 0.1% for subjects who received cethromycin 300 mg QD. None of the subjects who received active controls experienced these types of events. Each of the specific treatment-emergent adverse events potentially associated with visual disturbances was experienced by ≤0.1% of all cethromycin-treated subjects.

All Phase 3 Controlled CAP Studies
In the 2 Phase 3 controlled CAP studies combined, only 1 subject in the cethromycin 300 mg QD group (0.2%) experienced a treatment-emergent adverse event potentially associated with visual disturbances; none of the subjects in the clarithromycin 250 mg BID group experienced this type of event.

Loss of Consciousness

All Phase 1 Studies Combined
In the Phase 1 studies combined, the incidence of treatment-emergent adverse events potentially associated with loss of consciousness was 1.3% for all cethromycin-treated subjects and 0.2% for subjects who received cethromycin 300 mg QD. None of the subjects who received placebo or active controls experienced these types of events. Among all cethromycin-treated subjects, the only specific treatment-emergent adverse event potentially associated with loss of consciousness experienced by ≥1% of subjects was syncope vasovagal (12 subjects; 1.0%); however, only 2 of these events were considered related to study drug.

All Phase 2/3 Studies Combined
In the Phase 2/3 studies combined, the incidence of treatment-emergent adverse events potentially associated with loss of consciousness was similar between all cethromycin-treated subjects (0.2%) and subjects who received active controls (0.2%). None of the subjects who received cethromycin 300 mg QD experienced these types of events. Each of the specific treatment-emergent adverse events potentially associated with loss of consciousness was experienced by ≤0.1% of all cethromycin-treated subjects.

All Phase 3 Controlled CAP Studies
In the 2 Phase 3 controlled CAP studies combined, only 1 subject in the clarithromycin 250 mg BID group (0.2%) experienced a treatment-emergent adverse event potentially associated with loss of consciousness; none of the subjects in the cethromycin 300 mg QD group experienced this type of event.

Exacerbation of Myasthenia Gravis

All Phase 1 Studies Combined
In the Phase 1 studies combined, the incidence of treatment-emergent adverse events potentially associated with exacerbation of myasthenia gravis, which also included events of visual disturbance previously presented, was 0.8% for all cethromycin-treated subjects and 0.6% for subjects who received cethromycin 300 mg QD. The incidence of these events was 0.9% for placebo subjects and 0% for subjects who received active controls. Each of the specific treatment-emergent adverse events potentially associated with exacerbation of myasthenia gravis was experienced by ≤0.2% of all cethromycin-treated subjects.

All Phase 2/3 Studies Combined

In the Phase 2/3 studies combined, the incidence of treatment-emergent adverse events potentially associated with exacerbation of myasthenia gravis was similar between all cethromycin-treated subjects (0.8%) and subjects who received active controls (0.6%). The incidence of these types of events in subjects who received cethromycin 300 mg QD was 1.0%. Each of the specific treatment-emergent adverse events potentially associated with exacerbation of myasthenia gravis was experienced by ≤0.4% of all cethromycin-treated subjects.

All Phase 3 Controlled CAP Studies

In the 2 Phase 3 controlled CAP studies combined, the incidence of treatment-emergent adverse events potentially associated with exacerbation of myasthenia gravis was 1.1% for subjects who received cethromycin 300 mg QD and 0.4% for subjects who received clarithromycin 250 mg BID. Each of the specific treatment-emergent adverse events potentially associated with exacerbation of myasthenia gravis was experienced by ≤0.4% of cethromycin-treated subjects.

A summary of treatment-emergent adverse events of special interest potentially associated with exacerbation of myasthenia gravis by treatment group in the 2 Phase 3 controlled CAP studies combined is presented in Table 7.5.

Table 7.5: Treatment-Emergent Adverse Events of Special Interest Potentially Associated with Exacerbation of Myasthenia Gravis by Treatment Group (All Phase 3 Controlled CAP Studies)

	Cethromycin	Clarithromycin
Search Criteria	**300 mg QD**	**250 mg BID**
Preferred Term	**(N=548)**	**(N=548)**
Subjects with at least 1 TEAE potentially	6 (1.1)	2 (0.4)
associated with exacerbation of myasthenia		
gravis		
Dysphonia	2 (0.4)	0
Muscle Spasms	2 (0.4)	2 (0.4)
Muscular Weakness	1 (0.2)	0
Vision Blurred	1 (0.2)	0

mg=milligrams; QD=once daily; BID=twice daily; TEAE=treatment-emergent adverse event
Note: Percentages are displayed in parentheses. Applicant's data

Clinical Laboratory Evaluations

In the analyses of laboratory parameters, notable differences for possibly clinically significant values and shifts from baseline are defined as those events that have at least a 2.0 percentage point difference and at least a doubling of incidence between the treatment groups being compared. Any trends noted with respect to mean changes from baseline are discussed.

Hematology

All Phase 1 Studies Combined

In the Phase 1 studies combined, no notable differences were observed for the incidences of possibly clinically significant hematology values between all cethromycin-treated subjects and subjects who received placebo or active controls. Similarly, no notable differences were observed for the incidences of possibly clinically significant hematology values between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD.

All Phase 2/3 Studies Combined

In the Phase 2/3 studies combined, no notable differences were observed for the incidences of possibly clinically significant hematology values between all cethromycin-treated subjects and subjects who received active controls. Similarly, no notable differences were observed for the incidences of possibly clinically significant hematology values between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD.

In the Phase 2/3 studies combined, the incidences of treatment-emergent possibly clinically significant hematology values were similar among the cethromycin dose groups (<300 mg TDD, 300 mg TDD, 300 mg QD, and >300 mg TDD) with no notable differences observed with respect to increasing dose.

All Phase 3 Controlled CAP Studies Combined

In the 2 Phase 3 controlled CAP studies combined, no notable differences were observed for the incidences of possibly clinically significant hematology values between subjects who received cethromycin 300 mg QD or clarithromycin 250 mg BID.

Chemistry

All Phase 1 Studies Combined

In the Phase 1 studies combined, the only notable difference observed between all cethromycin-treated subjects and subjects who received placebo or active controls was for the incidences of possibly clinically significant increases in direct bilirubin values, which were higher in subjects who received active controls (4.26%) compared to all cethromycin-treated subjects (1.36%) and subjects who received placebo (0%). The incidences of possibly clinically significant chemistry values were similar between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD.

All Phase 2/3 Studies Combined

In the Phase 2/3 studies combined, no notable differences were observed for the incidences of possibly clinically significant chemistry values between all cethromycin-treated subjects and subjects who received active controls. Similarly, no notable differences were observed for the incidences of possibly clinically significant chemistry values between all cethromycin-treated subjects and subjects who received cethromycin

300 mg QD. Although not meeting the criteria of a notable difference, the incidences of increases in AST and ALT values were slightly higher in all cethromycin-treated subjects (1.02% and 1.30%, respectively) compared to active controls (0.33% and 0.73%, respectively); greater numbers of subjects who received cethromycin 300 mg QD had increases in these values (1.95% and 2.97%, respectively) compared to all cethromycin-treated subjects.

In the Phase 2/3 studies combined, the incidences of treatment-emergent possibly clinically significant chemistry values were similar among the cethromycin dose groups (<300 mg TDD, 300 mg TDD, 300 mg QD, and >300 mg TDD), except for a notable difference for the incidence of elevated BUN values, which were higher among subjects in the >300 mg TDD group (9.01%) compared with subjects who received the lower doses (<300 mg TDD: 0.82%; 300 mg QD: 2.07%). This pattern was not observed for possibly clinically significant creatinine values.

All Phase 3 Controlled CAP Studies Combined

In the 2 Phase 3 controlled CAP studies combined, notable differences observed between subjects who received cethromycin 300 mg QD or clarithromycin 250 mg BID were for the incidences of possibly clinically significant increases in AST values and decreases in albumin values, with cethromycin subjects having higher incidences of these values (2.98% and 3.40%, respectively) compared to clarithromycin subjects (0.67% and 1.08%). Although not meeting the criteria of a notable difference, the incidence of increases in ALT values was also higher in cethromycin subjects (3.78%) compared to clarithromycin subjects (1.97%). A summary of treatment-emergent possibly clinically significant AST, ALT, and albumin values in the 2 Phase 3 controlled CAP studies combined is presented by treatment group in Table 7.6.

Table 7.6: Treatment-Emergent Possibly Clinically Significant AST, ALT, and Albumin Values by Treatment Group (All Phase III Controlled CAP Studies)

Variable (PCS Criteria)	Cethromycin 300 mg QD (N=548)	Clarithromycin 250 mg BID (N=548)
AST (≥3 × ULN)	14/470 (2.98)	3/448 (0.67)
ALT (≥3 × ULN)	18/476 (3.78)	9/457 (1.97)
Albumin (≤25 g/L)	16/471 (3.40)	5/461 (1.08)

PCS=possibly clinically significant; mg=milligrams; QD=once daily; BID=twice daily; AST=aspartate aminotransferase;
ALT=alanine aminotransferase
Note: Percentages are displayed in parentheses.
Applicant's data

Mean Change From Baseline

All Phase 2/3 Studies Combined
In the Phase 2/3 studies combined, mean changes from baseline to the final on-therapy visit or the final off-therapy visit in chemistry values were generally small among all cethromycin-treated subjects and subjects who received active controls. Slight trends were observed in mean changes from baseline to the final on-therapy visit in ALT, creatinine, and uric acid values. Among all cethromycin-treated subjects, the mean increases in ALT, creatinine, and uric acid values at the final on-therapy visit were 3.83 U/L, 2.048 μ mol/L, and 11.539 μ mol/L, respectively, compared with an increase in ALT of 1.599 U/L and decreases in creatinine and uric acid of -3.187 μ mol/L and -14.336 μ mol/L for subjects who received active controls. Mean changes from baseline at the final off-therapy visit were similar between cethromycin and active control subjects for these variables. Compared to all cethromycin-treated subjects, subjects who received cethromycin 300 mg QD had higher mean increases in ALT values (6.793 vs. 3.83 U/L) at the final on-therapy visit; however, similar mean decreases in ALT values were noted in both groups at the final off-therapy visit.

All Phase 3 Controlled CAP Studies Combined
In the 2 Phase 3 controlled CAP studies combined, mean changes from baseline to the final on-therapy visit or the final off-therapy visit in chemistry values were generally small among subjects who received cethromycin 300 mg QD or clarithromycin 250 mg BID. Slight trends were observed in mean changes from baseline to the final on-therapy visit in ALT, AST, creatinine, and uric acid values. Among cethromycin-treated subjects, the mean increases in ALT, AST, creatinine, and uric acid values at the final on-therapy visit were 6.961 U/L, 2.121 U/L, 2.757 μ mol/L, and 9.212 μ mol/L, respectively, compared with smaller increases in ALT (2.107 U/L) and uric acid (1.39 μ mol/L) and decreases in creatinine (-5.127 μ mol/L) and AST (-2.103 U/L) for subjects who received clarithromycin. Mean changes from baseline at the final off-therapy visit were similar between the cethromycin and clarithromycin groups for these variables.

In the 2 Phase 3 controlled CAP studies, a total of 518 subjects had blood samples collected for cethromycin plasma concentrations. Of these, 281 had their blood samples collected at the time of predicted C_{max} (Visit 2, between 2 and 4 hours post-dose). The mean plasma concentration was 1011±1127 ng/mL among all 518 subjects and 1250±1233 ng/mL among the 281 C_{max} subjects. Cethromycin plasma concentrations were plotted against ALT values obtained at Evaluation 2. There was no linear relationship between ALT values and cethromycin plasma concentrations.

Urinalysis

All Phase 1 Studies Combined
In the Phase 1 studies combined, no notable differences were observed for the incidences of possibly clinically significant urinalysis values between all cethromycin-treated

subjects and subjects who received placebo or active controls. Similarly, no notable differences were observed for the incidences of possibly clinically significant urinalysis values between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD.

All Phase 2/3 Studies Combined
In the Phase 2/3 studies combined, no notable differences were observed for the incidences of possibly clinically significant urinalysis values between all cethromycin-treated subjects and subjects who received active controls. Similarly, no notable differences were observed for the incidences of possibly clinically significant urinalysis values between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD.

In the Phase 2/3 studies combined, the incidences of treatment-emergent possibly clinically significant urinalysis values were similar among the cethromycin dose groups (<300 mg TDD, 300 mg TDD, 300 mg QD, and >300 mg TDD), with no notable differences observed with respect to increasing dose.

All Phase 3 Controlled CAP Studies
In the 2 Phase 3 controlled CAP studies combined, no notable differences were observed for the incidences of possibly clinically significant urinalysis values between subjects who received cethromycin 300 mg QD or clarithromycin 250 mg BID.

Vital Signs

In the analyses of vital sign parameters, notable differences for possibly clinically significant values and shifts from baseline are defined as those events that have at least a 2.0 percentage point difference and at least a doubling of incidence between the treatment groups being compared. Any trends noted with respect to mean changes from baseline are discussed.

All Phase 1 Studies Combined
In the Phase 1 studies combined, no notable differences were observed between all cethromycin-treated subjects and subjects who received placebo for the incidences of possibly clinically significant vital signs values. However, a notable difference was observed between all cethromycin-treated subjects and subjects who received active controls for the incidence of possibly clinically significant increases in temperature, which was higher in all cethromycin-treated subjects (5.03%) compared to subjects who received active controls (0%). The incidences of possibly clinically significant vital signs values were similar between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD.

All Phase 2/3 Studies Combined
In the Phase 2/3 studies combined, no notable differences were observed for the incidences of possibly clinically significant vital signs values between all cethromycin-

treated subjects and subjects who received active controls. Similarly, no notable differences were observed for the incidences of possibly clinically significant vital signs values between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD.

All Phase 3 Controlled CAP Studies Combined
In the 2 Phase 3 controlled CAP studies combined, no notable differences were observed for the incidences of possibly clinically significant vital signs values between subjects who received cethromycin 300 mg QD or clarithromycin 250 mg BID.

Cardiac Safety

Electrocardiograms (ECGs)

An extensive evaluation of the potential effect of cethromycin on QT interval duration has been performed. Preclinical studies indicated minor QT prolongation in conscious dogs at free plasma levels 70-fold above the mean human free plasma maximum concentration of drug (C_{max}) at a dose of 300 mg QD. Two Phase I studies were specifically conducted to assess the effect of cethromycin on QT intervals in addition to the ECG data obtained from 47 of the 49 studies conducted in the cethromycin clinical program. Results of the 2 individual QT studies are presented, and also results of the pooled analyses for the Phase 1 studies, the Phase 2/3 studies, and the 2 Phase 3 controlled CAP studies are presented below.

Phase 1 Individual QT Studies
Two Phase 1 studies were conducted to determine the effect of cethromycin on QT intervals.

The first study (M01-325) was conducted between 2001-2002 by Abbott Laboratories. In 2007, Advanced Life Sciences conducted a "thorough QT/QT_C study" (CL07-001) following the ICH E14 guidance for clinical evaluation of QT/QT_C interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs.

Study M01-325: An Evaluation of the Effect on the QT Interval of Cethromycin in Healthy Adult Subjects
Study M01-325 was a Phase 1, randomized, double-blind, placebo-controlled, multiple-dose, 4-period complete crossover study in adult male and female subjects who were 18 years of age or older to evaluate the effect on the QT interval of 150 mg BID, 300 mg BID, and 450 mg BID of cethromycin in healthy subjects. Subjects were to receive 1 of 4 sequences of the following regimens administered BID for 5 consecutive days: Regimen A (placebo), Regimen B (cethromycin 150 mg), Regimen C (cethromycin 300 mg), and Regimen D (cethromycin 450 mg). A total of 68 subjects were entered into the study (17 for each of the 4 sequence groups). In October 2001, clinically asymptomatic elevations in liver enzymes were observed in 2 subjects in the 150 mg BID regimen and 2 subjects in the 450 mg BID regimen. The study was interrupted for safety analysis of liver enzyme

values from prior Phase 1 and Phase 2 studies and available data from Phase 3 studies. Following discussion with the Food and Drug Administration (FDA), the study was resumed with the discontinuation of the cethromycin 450 mg BID regimen. Overall, 27 subjects completed the study (9 completed all 4 periods and 18 completed 3 periods after removal of the cethromycin 450 mg BID regimen upon study resumption). Among the 41 subjects who did not complete the study, 4 were prematurely discontinued due to an adverse event, 1 subject was prematurely discontinued due to noncompliance, and 36 subjects did not return for dosing after study resumption. At the conclusion of the study, 39 subjects had received placebo, 37 subjects had received cethromycin 150 mg BID, 38 subjects had received cethromycin 300 mg BID, and 21 subjects had received 450 mg BID.

The incidences of treatment-emergent adverse events were 51% in the placebo regimen, 57% in the cethromycin 150 mg BID regimen, 82% in the cethromycin 300 mg BID regimen, and 76% in the cethromycin 450 mg BID regimen. The incidences of adverse events judged by the investigator to be probably or possibly related to study drug were 26% in the placebo regimen; 41% in the cethromycin 150 mg BID regimen; 58% in the cethromycin 300 mg BID regimen; and 67% in the cethromycin 450 mg BID regimen. The probably or possibly treatment-related adverse events experienced by ≥3 subjects were diarrhea and headache in the placebo regimen, headache and taste perversion in cethromycin 150 mg BID regimen, dyspepsia, headache, flatulence, and taste perversion in the cethromycin 300 mg BID regimen, and taste perversion in the cethromycin 450 mg BID regimen. Taste perversion was the only adverse event that appeared to show dose dependence. No adverse events of arrhythmia, including Torsade de Pointes, were reported in this study. There were no deaths or other serious adverse events reported. Four cethromycin subjects (2 in the 150 mg BID regimen and 2 in the 450 mg BID regimen) were prematurely discontinued from the study due to elevated liver enzymes that were judged by the investigator as adverse events. All of the events were asymptomatic, self-limiting transaminase elevations (ALT/AST >3 × ULN), which returned to within normal limits, in 2-4 weeks without intervention. Transaminase elevations were accompanied by increased GGT, alkaline phosphatase, or LDH values in some cases, but no abnormalities in total bilirubin were observed. One of the subjects was subsequently found to have cholelithiasis with a stone at the level of the common bile duct on hepatic ultrasound. No other subjects in the study had clinically significant elevations in liver function tests. No hematology values were judged by the investigator to be an adverse event. No clinically important trends in physical examination results or vital signs were observed during the study.

No clinically significant abnormalities were seen in the uncorrected QT or any of the corrected (QT_c) intervals during the study. Three subjects had a prolonged QT or QT_c interval (as defined by the Committee for Proprietary Medicinal Products [CPMP]) and 3 subjects had a QT or QT_c value increased by >60 msec from baseline. These subjects remained asymptomatic and the QT/QT_c intervals returned to baseline at post-dose. An increase in QT_cB was probably related to the increases in heart rate observed in the study, since it is known that QT_cB is sensitive to changes in heart rate. With the individualized

correction, there was no statistically significant difference from placebo for the cethromycin doses, while the estimates of the differences of the means of the cethromycin doses from the placebo mean were all 2.6 msec or less.

Study CL07-001: A Double-Blind, Randomized, Parallel Trial to Define the ECG Effects of Cethromycin Using a Clinical and a Supratherapeutic Dose Compared to Placebo and Moxifloxacin (An Open-Label Positive Control) in Healthy Men and Women: A Thorough ECG Trial.
Study CL07-001 was a Phase 1, randomized, double-blind (except for the use of moxifloxacin), placebo and positive-controlled, multiple-dose, single-site, 4-arm, parallel-design using healthy adult male and female subjects 18-45 years of age, inclusive, to evaluate the effect of cethromycin on cardiac repolarization, as detected by QT/ QT_c prolongation in healthy subjects.

Two hundred thirty-eight subjects participated and were randomized to receive 1 of the following 4 treatment regimens:

Treatment A: Placebo from Day 1 through Day 5.
Treatment B: Placebo from Day 1 through Day 4, and 400 mg moxifloxacin on Day 5.
Treatment C: Cethromycin 300 mg QD from Day 1 through Day 5.
Treatment D: Cethromycin 900 mg QD from Day 1 through Day 5.

Electrocardiograms were obtained using a 12-lead continuous digital recorder on Day -1 (baseline) and on Day 5. A total of 39 ECGs were analyzed at baseline and on Day 5, for a total of 78 ECGs in each completed subject. Blood was obtained for pharmacokinetic sampling on Days 1 and 5.

Of the 238 subjects who participated in the study, 233 completed the study as planned. Three subjects (cethromycin 900 mg) prematurely discontinued due to adverse events, 1 subject (cethromycin 300 mg) was discontinued by the investigator due to abnormal laboratory results, and 1 subject (cethromycin 900 mg) withdrew due to personal reasons. No adverse events of arrhythmia, including Torsade de Pointes, or incidence of sudden death were reported in this study. Overall, nausea was the most common adverse event reported by a total of 52 (21.85%) subjects. Vomiting was the second most common adverse event reported by a total of 35 (14.71%) subjects. The majority of treatment-emergent adverse events were reported by subjects after the administration of Treatment D (cethromycin 900 mg). All adverse events were mild to moderate in severity. No deaths, other serious adverse events, or other significant adverse events occurred over the course of the study.

Since QT varies inversely by heart rate, the assessment of cardiac repolarization was defined by the QT_c interval. The primary endpoint was the individualized QT interval (QT_cI). The mean change from baseline for the QT_cI duration placebo-corrected using the time averaged analysis showed +1 msec for the clinical dose and +3 msec for the supratherapeutic dose of cethromycin.

Using the time matched primary analysis endpoint; no time point in the cethromycin dose groups showed an upper bound that was ≥10 msec. The specific outlier criteria included a new >500 msec QT_cI, a change from baseline of >60 msec or new abnormal U waves. No subject on cethromycin showed any of these criteria. The nonspecific criterion of a 30-60 msec change from baseline was seen in 2% on placebo, 7% on moxifloxacin, and in 2% of cethromycin subjects on either dose. No new morphological changes in this trial were observed except for the non-specific change in T-wave morphology which was observed in 3.4% on placebo, 3.4% on moxifloxacin, 0% on 300 mg cethromycin, and 1.8% on 900 mg cethromycin. There were no statistically significant differences between the sub-groupings by gender in this study.

The relationship between plasma concentrations of parent and metabolite and change in QT_cI revealed no evidence of any signal that cethromycin concentration or metabolite were related to observed QT_cI changes. The mean change from baseline in placebo-corrected heart rate for the moxifloxacin group was 1 bpm and for the clinical cethromycin dose group it was 12 bpm; neither change was clinically relevant. For the supratherapeutic dose of cethromycin, the heart rate change was 10 bpm which was clinically relevant and was associated with more tachycardic outliers (13%) compared to placebo (7%) and the clinical cethromycin dose (3%). Thus, the supratherapeutic dose does have a heart rate effect (marked increase) that prohibits use of the Bazett QT correction due to its known high degree of inaccuracy for drugs with this heart rate effect. The mean change from baseline placebo-corrected for PR interval for the moxifloxacin group and the clinical and supratherapeutic dose cethromycin groups were approximately -1, 0, and 0 msec, respectively; similarly for the QRS they were 0, -1, and -1 msec, respectively.

The results of this thorough ECG trial showed no signal of any effect on AV conduction, depolarization or cardiac repolarization as measured by the PR, QRS, QT_cI, or QT_cF interval durations. There was no effect on heart rate in the clinical dose at steady state on cethromycin, though in the supratherapeutic dose group, there was a 10 bpm increase requiring use of the primary QT_cI endpoint, or QT_cF, but not QT_cB for detection of any effect on cardiac repolarization. Cethromycin did not show any signal of any outlier imbalance. No changes in ECG wave form morphology were identified in the cethromycin group compared to placebo.

The validity of the trial was demonstrated by the fact that the moxifloxacin positive control group exhibited the expected small change in QT_c duration and that the placebo group's change from baseline was within 2 msec for QT_cI, providing solid evidence demonstrating that the spontaneous factors for QT_c change were well controlled.

Possibly Clinically Significant Electrocardiogram Values
The definitions of possibly clinically significant ECG values are presented in the following table:

Table 7.6: Possibly Clinically Significant Electrocardiogram Values

Electrocardiogram Variable	Direction	Criterion
Heart rate	Decrease	Decrease of more than 20% to a value <50 bpm
	Increase	Increase of more than 20% to a value >110 bpm
PR Interval	Decrease	Decrease of more than 25%
	Increase	Increase of more than 25%
QRS Interval	Decrease	Decrease of more than 25%
	Increase	Increase of more than 25%
QT_C Interval	Prolonged	Male: value >450 msec Female: value >470 msec
	Very High	Value >500 msec or an increase of >60 msec

All Phase 1 Studies Combined

In the Phase 1 studies combined, no notable differences were observed between all cethromycin-treated subjects and subjects who received placebo for the incidences of possibly clinically significant ECG values. However, a notable difference was observed between all cethromycin-treated subjects and subjects who received active controls for the incidence of possibly clinically significant decreases in heart rate, which was higher in all cethromycin-treated subjects (2.0%) compared to subjects who received active controls (0%). The incidences of possibly clinically significant ECGs values were similar between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD. None of the episodes that met the possibly clinically significant criteria for prolonged or very high QT_c interval were reported as treatment-emergent serious adverse events or resulted in discontinuation.

All Phase 2/3 Studies Combined

In the Phase 2/3 studies combined, no notable differences were observed for the incidences of possibly clinically significant ECG values between all cethromycin-treated subjects and subjects who received active controls. Similarly, no notable differences were observed for the incidences of possibly clinically significant ECG values between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD. In the Phase 2/3 studies combined, none of the episodes that met the possibly clinically significant criteria for prolonged or very high QT_c interval were reported as treatment-emergent serious adverse events or resulted in discontinuation.

In the Phase 2/3 studies combined, the incidences of treatment-emergent possibly clinically significant ECG values were similar among the cethromycin dose groups (<300 mg TDD, 300 mg TDD, 300 mg QD, and >300 mg TDD) for increases and decreases in heart rate, decreases in PR intervals, and prolonged QT_c (Bazett and Fridericia). The incidences of increases in PR intervals and increases and decreases in QRS intervals tended to decrease with increasing dose, with notably higher values for subjects who received cethromycin <300 mg TDD (7.43%, 9.05%, and 4.46%, respectively) compared to those who received the higher doses (300 mg QD: 3.21%, 4.58%, and 2.14%; >300 mg TDD: 1.89%, 1.89% and 0.63%, respectively). Although the incidence of prolonged QT_c was generally similar among the cethromycin dose groups, the incidences of very high

QT_c intervals (Bazett and Fridericia) were notably higher in the cethromycin >300 mg TDD group (5.03% and 4.4%, respectively) compared with the lower doses (300 mg QD: 1.68% and 1.98%; <300 mg TDD: 2.33% and 2.05%, respectively).

All Phase 3 Controlled CAP Studies Combined
In the 2 Phase 3 controlled CAP studies combined, no notable differences were observed for the incidences of possibly clinically significant ECG values between subjects who received cethromycin 300 mg QD or clarithromycin 250 mg BID. In the 2 Phase 3 controlled CAP studies combined, none of the episodes that met the possibly clinically significant criteria for prolonged or very high QT_c interval were reported as treatment-emergent serious adverse events or resulted in discontinuation.

Mean Change From Baseline in Electrocardiogram Parameters

All Phase 2/3 Studies Combined
In the Phase 2/3 studies combined, mean changes from baseline to the final on-therapy visit or the final off-therapy visit in ECG values were generally small, and no discernable trends were observed between all cethromycin-treated subjects and subjects who received active controls. In addition, no discernable trends were observed in mean changes from baseline in ECG values between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD.

All Phase 3 Controlled CAP Studies Combined
In the 2 Phase 3 controlled CAP studies combined, mean changes from baseline to the final on-therapy visit or the final off-therapy visit in ECG values were small, and no discernable trends were observed between subjects who received cethromycin 300 mg QD or clarithromycin 250 mg BID.
In the 2 Phase 3 controlled CAP studies, a total of 518 subjects had blood samples collected for cethromycin plasma concentrations. Of these, 281 had their blood samples collected at the time of predicted C_{max} (Visit 2, between 2 and 4 hours post-dose). The mean plasma concentration was 1011±1127 ng/mL among all 518 subjects and 1250±1233 ng/mL among the 281 C_{max} subjects. Cethromycin plasma concentrations were plotted against changes from baseline in QT_cB values obtained at Evaluation 2. There was no linear relationship between changes in QT_cB and cethromycin plasma concentrations.

Reviewer's Comments:
The above discussion of cardiac safety is based on the applicant's evaluation of their ECG studies. At the time this briefing document was prepared, the review of the QT interdisciplinary review team was pending. Preliminary findings raised questions about the applicant's individual QT correction methodology, and suggested that there is a dose and exposure-dependent increase in QTcI with cethromycin. QTc effects of cethromycin will be included in the safety discussion at the upcoming advisory committee meeting.

Safety in Subgroups

Intended Label Dose Range Group

Total daily doses of cethromycin <300 mg were received by 2219 subjects and >300 mg were received by 757 subjects. A total of 1375 subjects received cethromycin 300 mg QD, the dose for which approval is sought.

Among all cethromycin-treated subjects in the Phase 1, 2, and 3 studies combined, the majority completed study participation (89.3%). Subject disposition was similar between all cethromycin-treated subjects and subjects who received cethromycin 300 mg QD. Among subjects who received cethromycin 300 mg QD in the Phase 1, 2, and 3 studies combined, the majority completed study participation (92.9%).

Intrinsic Factors

Results of Phase 1 studies indicate no dose adjustment is required when cethromycin is administered to subjects with mild or moderate hepatic impairment. In subjects with severe renal impairment, the dose of cethromycin should be lowered.

In the 2 Phase 3 controlled CAP studies combined, the treatment-emergent adverse event profile of cethromycin was consistent across demographic characteristics including gender, race, age, and Fine criteria. Additionally, no clinically important differences were observed between the cethromycin and clarithromycin groups when the incidences of possibly clinically significant laboratory values were analyzed by gender and age. A history of cardiac disease, hepatic disease, or diabetes had no clinically important effect on the treatment-emergent adverse event profile of cethromycin.

Extrinsic Factors

In the 2 Phase 3 controlled CAP studies combined, the treatment-emergent adverse event profile of cethromycin was consistent across regions, alcohol use, and tobacco use.

Drug Interactions

Results of Phase 1 drug interaction studies showed increases in cethromycin exposure with the potent CYP3A inhibitor, ketoconazole (Study M99-138), and decreases in cethromycin exposure with the potent CYP3A4 inducer, rifampin (Study M00-156). Cethromycin affected midazolam (Study M00-155) pharmacokinetics to a much lesser extent than did ketoconazole, erythromycin or clarithromycin. Due to the interaction of cethromycin with theophylline (Study M99-139), digoxin (Study M00-263), and warfarin (Study M00-264), plasma levels of these agents may require monitoring. Doses of digoxin and warfarin may need to be adjusted given the narrow therapeutic index of these medications.

Based on results of the Phase 2 drug interaction studies, the exclusion criteria for the Phase 3 controlled CAP studies prevented concomitant administration of several drugs that would have possibly interacted with CYP3A. As a result of this exclusion, no

meaningful analyses could be performed for drug-drug interactions in the Phase 3 controlled CAP studies.

Pediatrics and Effect on Growth
Advanced Life Sciences has requested a partial waiver of pediatric CAP studies in the age groups that span neonates to children < 8 years of age. The reason for this waiver request is an inability to develop an acceptable (bioequivalent and taste masking) suspension or other liquid formulation.

In accordance with FDA's request made at the pre-NDA meeting on April 7, 2008, Advanced Life Sciences has provided a pediatric development plan. Further justification of this waiver request is given in the pediatric development plan.

Request for deferral of pediatric studies
Advanced Life Sciences has requested a deferral of pediatric CAP studies in the age groups spanning 8-18 years of age. Before commencing clinical studies in the pediatric patient population, Advanced Life Sciences wishes to complete the adult clinical program in order to first evaluate the safety and efficacy of cethromycin in the adult patient population.

Use in Pregnancy and Lactation
There was no evidence of cethromycin-related teratogenicity in rats or rabbits at maternotoxic doses. Fertility was not affected in female rats. F1 rat pups exhibited decreased body weights (and delayed eye opening and pinna detachment) at maternotoxic doses.

There were no adequate and well-controlled studies in pregnant women. During the cethromycin clinical program, 2 female subjects treated with cethromycin reported unintended pregnancies. Both subjects were treated in Phase 2/3 Study M00-225, which was a randomized, double-blind study to determine the safety and efficacy of cethromycin 150 mg QD or BID for 10 days for the treatment of sinusitis.

• Subject 16805-40043 was a 30-year-old female who received cethromycin 150 mg QD for 10 days. The subject had a negative pregnancy test at baseline. Twenty-nine days after her last dose of study drug, she had an adverse event of pregnancy reported. No follow-up information regarding the pregnancy was available.

• Subject 12264-40107 was a 32-year-old female who received cethromycin 150 mg BID for 11 days. The subject had a negative pregnancy test at baseline. Twenty-eight days after her last dose of study drug, she had an adverse event of pregnancy reported. No follow-up information regarding the pregnancy was available.

Neither subject reported the use of oral contraceptives prior to or during the study and their actual method of birth control were not collected as part of the study data.

Two subjects (Subjects 12528-11325 and 9377-11294) who were treated with penicillin V in Study M00-223 (pharyngitis) became pregnant after completing therapy. Both subjects had negative pregnancy tests at study entry. One of these subjects had an induced abortion and no follow-up information regarding the pregnancy was available for the other subject.

Overdose
Cethromycin was acutely toxic only at highly exaggerated doses in mice and rats, suggesting that it has little acute overdose potential. Given the emesis seen after high oral doses in monkeys, and the extreme sensitivity to the emetic effect of cethromycin in dogs, the potential for overdose appears to be limited.

One subject in the cethromycin clinical program experienced an adverse event of accidental overdose. In Phase 1 Study M00-262, Subject #119 was assigned to receive cethromycin 150 mg QD for 5 days. However, the subject misunderstood the dosing procedure and ingested all 5 tablets (750 mg) as a single dose on Day 1. Approximately 4 hours after ingestion of the dose, the subject experienced sporadic episodes of diarrhea that lasted for 20 hours, which was considered mild in intensity and probably related to study drug. The subject also experienced taste perversion that lasted for 3 days, which was considered moderate in intensity and probably related to study drug. The subject was prematurely discontinued from the study with no subsequent events.

Drug Abuse
There is no evidence for and no anticipation of subject abuse of cethromycin.

Withdrawal and Rebound
There has been no evidence of withdrawal effects following use of the ketolide class of compounds. Physiological or psychological changes on withdrawal from these drugs have not been demonstrated. No withdrawal effects have been noted during the conduct of the cethromycin clinical program.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability
There is no evidence that cethromycin treatment will interfere with the ability to drive, operate machinery, or impair mental ability. The incidence of adverse events such as dizziness, vertigo, and syncope, were low and similar between subjects who received cethromycin or active controls.

Postmarketing Data
Not applicable.

VIII. ISSUES FOR DISCUSSION

1. Do the data presented demonstrate the safety of cethromycin for the treatment of community-acquired pneumonia?

- If your answer is yes, are there any particular issues that warrant specific mention in product labeling?
- If your answer is no, what additional data/studies are needed?

2. Do the data presented demonstrate the efficacy of cethromycin for the treatment of community-acquired pneumonia?

- If your answer is no, what additional data/studies are needed?

IX. APPENDICES

Appendix 1 – Draft Guidance for Industry – Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment

Appendix 2 – Microbiology Table